Recent Advances in Cancer Therapy Targeting Proteins Involved in DNA Double-Strand Break Repair
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Abstract
Damage to genetic material represents a persistent and ubiquitous threat to genomic stability. Once DNA damage is detected, a multifaceted signaling network is activated that halts the cell cycle, initiates repair, and in some instances induces apoptotic cell death. In this article, we will review DNA damage surveillance networks, which maintain the stability of our genome, and discuss the efforts underway to identify chemotherapeutic compounds targeting the core components of DNA double-strand breaks (DSB) response pathway. The majority of tumor cells have defects in maintaining genomic stability owing to the loss of an appropriate response to DNA damage. New anticancer agents are exploiting this vulnerability of cancer cells to enhance therapeutic indexes, with limited normal tissue toxicity. Recently inhibitors of the checkpoint kinases Chk1 and Chk2 have been shown to sensitize tumor cells to DNA damaging agents. In addition, the treatment of BRCA1- or BRCA2-deficient tumor cells with poly(ADP-ribose) polymerase (PARP) inhibitors also leads to specific tumor killing. Due to the numerous roles of p53 in genomic stability and its defects in many human cancers, therapeutic agents that restore p53 activity in tumors are the subject of multiple clinical trials. In this article we highlight the proteins mentioned above and catalog several additional players in the DNA damage response pathway, including ATM, DNA-PK, and the MRN complex, which might be amenable to pharmacological interventions and lead to new approaches to sensitize cancer cells to radio- and chemotherapy. The challenge is how to identify those patients most receptive to these treatments. (Clin Cancer Res 2009;15(20):6314–20)

Background
The importance of a robust DNA-damage surveillance network is underscored by the fact that defects in signaling and repair of DNA damage are causally linked with the development of genomic instability and human cancer. For example, mutation of the ATM kinase, central to cell cycle checkpoint activation after double-strand breaks (DSBs), leads to the cancer-prone syndrome ataxia telangiectasia (1). In addition, mutation of meiotic recombination 11 (Mre11) or NBS1, components of the DSB-sensing MRN (comprised of Mre11, Rad50, and NBS1) complex, leads to the genomic instability syndromes ataxia-telangiectasia-like-disorder (AT-LD) and Nijmegen Breakage syndrome (NBS), respectively (2).

Detailed description of the DNA damage response is beyond the scope of this article and the reader is referred to several excellent treatises on DNA damage responses (3–6). Only the features of DNA DSB signaling and repair, which are potential targets for therapeutic applications, will be highlighted here.

A wide variety of DNA lesions elicit the activation of cell cycle checkpoints, controlled by the ATM and ATR kinases (7). The sensors of DNA-damage signaling that activate ATM and ATR by recruiting them to sites of DNA damage include the MRN complex and Replication Protein A (RPA)-coated single-stranded DNA (ssDNA), respectively. ATM activation is indicated by its autophosphorylation, its recruitment to chromatin, and conversion from a dimer to a monomeric form (8). A number of proteins are required for maximal activation of ATM, these include hSSB1 and the MRN complex (9, 10). Once activated ATM phosphorylates downstream effector proteins to initiate cell cycle checkpoints at the G1/S, intra-S, and G2/M boundaries. The activation of these checkpoints allows repair of DNA damage before it is replicated and passed on to daughter cells and therefore preserves the genomic integrity. Checkpoint proteins 1 and 2 (Chk1 and Chk2) are key downstream checkpoint substrates of ATM and ATR (Fig. 1). During checkpoint activation Chk1 and Chk2 phosphorylation is necessary for the activation of the DNA damage checkpoints (11, 12). In order to activate the checkpoints and stall the cell cycle, Chk1 or Chk2 phosphorylate several downstream substrates (see review article, ref. 13, for further details).

Activated ATM also contributes toward the phosphorylation of the tumor suppressor protein p53 on serine 15, which
in turn transactivates the kinase inhibitor p21, leading to the inhibition of two cyclin-dependent kinases, Cyclin E/A-Cdk2, which stall the cell cycle at the G1/S boundary (Fig. 1). p53 also plays a role in maintaining the G2/M checkpoint via transactivation of p21. Other substrates involved in checkpoint activation that are phosphorylated by ATM include Mre11, NBS1, RPA34, mediator of the damage checkpoint 1 (MDC1), structural maintenance of chromatin 1 (SMC1), and BRCA1 (14).

DNA DSBs are perhaps the biggest threat to genomic stability. Unrepaired DSBs can lead to cell death, whereas incorrectly repaired DSBs have the potential to produce chromosomal translocation and genomic instability. There are two main pathways of DSB repair, nonhomologous end joining (NHEJ) and homology-directed repair (HR).

In mammalian cells, the majority of ionizing radiation (IR)-induced DSBs are repaired by NHEJ. NHEJ occurs mainly in the G0 and G1 phase of the cycle (Fig. 1). It is responsible for the repair of spontaneous DSBs induced by agents such as IR and programmed DSBs generated during generation of T-cell receptors and immunoglobulin molecules via V(D)J recombination. NHEJ involves rejoining of the two broken ends of the DNA in a sequence-independent manner. Consequently NHEJ is sometimes viewed as a more error prone method of DSB repair as genetic information can be lost in the repair of staggered breaks. NHEJ requires coordination of many proteins and signaling pathways. One of the main proteins involved in this repair pathway is DNA-dependent protein kinase (DNA-PK). The Ku70/80 heterodimer component of DNA-PK binds to the two DNA ends in a ring conformation. The DNA binding of Ku70/80 and alignment of the two DNA ends subsequently activates the catalytic activity of DNA-PK, which promotes the ligation of DNA ends by the XRCC4-Ligase IV complex. The recently identified NHEJ component, XRCC4-like factor (XLF), stimulates the activity of the XRCC4-DNA ligase IV complex toward noncompatible DNA ends (15). DNA end-processing enzymes such as Artemis are also required for the processing of a subset of IR-induced DSBs in vivo (16).

HR is the second major pathway for the repair of DSBs in mammalian cells. It functions only during the late S and G2 phases of the cell cycle, when a homologous region of DNA is available (Fig. 1). HR uses the homologous template to faithfully repair the DNA, and consequently, it is a more accurate form of DSB repair. HR is the predominant pathway of repair of endogenous DSBs that are produced when replication fork collapse occurs (see several reviews on this topic; refs. 4, 17, 18).

Following induction of a DSB, one of the first events to occur is resection of the break in a 5′-3′ dependent manner to produce long stretches of ssDNA, which acts as a signal to recruit other DNA damage repair proteins. The MRN complex, one of the central components of HR is stimulated to initiate resection in the early stages of HR by an interaction with CtIP (19). A
of this idea was initially borne out when a high-throughput DNA repair pathway was suggested to be involved in cancer treatment. Validation of the ATM-mediated pathway may also sensitize cells deficient in clinical treatment. There is also an indication that inhibitors of DDR pathway may preferentially sensitize p53 deficient tumor cells to radiation and chemotherapy. This finding stimulated interest in the development and testing of Chk1 and Chk2 inhibitors that may show antitumor properties when combined with other chemotherapeutics. One potential clinical challenge for the use of UCN-01 as a tumor treatment is the sensitization of normal tissues due to the broad spectrum of its targets. Increased myelosuppression was seen in the phase I clinical trials of UCN01 with topotecan at lower doses than when topotecan was used alone (29, 30). With increasingly selective inhibitors and biomarkers it is likely that better therapeutic indexes can be achieved in clinical settings.

Several specific inhibitors of the Chk1 and Chk2 kinases have now emerged including AZD7762 (AstraZeneca), XL844 (Exelixis), and PF-00477736 (Pfizer). Although these compounds all inhibit Chk1 and Chk2 at various concentrations, PF-00477736 displays the greatest specificity for Chk1. Notably, treatment with PF-00477736 also leads to strong inhibition of Chk1 auto-phosphorylation, in contrast to the other checkpoint kinase inhibitors. It is unclear what effect these differences will have in a clinical setting, but it has been previously shown that inhibition of Chk1 may increase the toxicity of DNA damaging agents. These inhibitors have been shown to sensitize cancer cells and xenografts to anticancer damaging agents (31–34). Several clinical trials using Chk1 and Chk2 inhibitors as antitumor agents in combination with genotoxic agents including gemcitabine, irinotecan, and cisplatin targeting many tumor subsets are currently underway (see Table 1 for further information). Together, these studies further support the potential of checkpoint kinase inhibitors to enhance the efficacy of both conventional chemotherapy and radiotherapy and increase tumor regression and tumor cell cytotoxicity in a subset of cancers.

Recent advances have also implicated checkpoint pathway activation as a major mechanism driving radioresistance in cancer stem cells. Glioblastoma is one of the most lethal human malignancies, but its treatment remains restricted because of the radioresistance found in this subset of tumors. Strikingly, the radioresistance of glioma stem cells could be reversed by the addition of a specific Chk1 and Chk2 inhibitor (de bromohymenialdisine; ref. 35), highlighting the potential of inhibiting checkpoint responses to overcome the resistance of cancer stem cells to radiotherapy.

Inactivation of p53 is a crucial event during the onset of tumorigenesis with approximately 50% of all human cancers containing somatic mutations in the p53 gene (36). A major

**Clinical-Translational Advances**

DNA damage remains the mainstay of cancer treatment, however the toxic side effects of agents that induce DNA damage limit the dose that can be tolerated and the degree of tumor death that can be achieved. Mutations in genes required for the detection, signaling, and repair of DNA damage can lead to increased DNA damage, incorrect repair of DNA damage, and cancer (3). To compensate for the loss of specific DNA repair pathways, different or faulty DNA repair pathways may be induced to enable tumor cells to survive. The activation of other repair pathways has been suggested to be responsible for the limited response of tumors to radio- and chemotherapy. If the DNA repair pathways essential for a tumor's survival can be identified and disrupted, this will allow chemotherapy to be much more efficient. Thus, it can be argued that targeting both checkpoint and repair pathways in combination may selectively kill tumor cells over healthy cells. Below we catalog several players in the DNA-damage response pathway that might be amenable to pharmacological interventions.

ATM is the predominant kinase responsible for the activation of multiple cell cycle checkpoints following DSB induction. The intricacies of the ATM-mediated signaling network were highlighted by a recent study showing that hundreds of phosphorylation events are dependent upon the ATM kinase (14). The first suggestion that ATM may be an attractive target for chemotherapy was that cells from patients with the genomic instability disorder ataxia telangiectasia, resulting from a mutation in the ATM gene, were exquisitely sensitive to radiation (1). In addition, caffeine (a known inhibitor of ATM) could increase cellular sensitivity to radiation and chemotherapeutic drugs (24, 25), although its lack of specificity and potency makes it unsuitable as a clinical agent. LY294002 is another ATM inhibitor, which broadly inhibits the kinase activity of PIKKs. Like caffeine the widespread use of LY294002 has been restricted by its lack of specificity, however, it has been used as a research tool for the design of more specific PIKK inhibitors.

A highly specific small molecule ATP competitive inhibitor of ATM named KU-55933 was identified via screening of a drug library based on LY294002 (26). This compound can efficiently sensitize tumor cells to radiation and DSB-inducing chemotherapeutic agents, such as camptothecin and etoposide, and there are suggestions that this compound may be used as a potential clinical treatment. There is also an indication that inhibitors of the ATM-mediated pathway may also sensitize cells deficient in other DNA repair pathways to cancer treatments. Validation of this idea was initially borne out when a high-throughput siRNA screen identified ATM as a target that disrupted the growth of cells deficient in the Fanconi anemia (FA) pathway (27). Inhibition of ATM via siRNA was lethal to cells with a defective FA pathway. Because FA genes are disrupted in a range of cancers, the inhibition of ATM may provide a successful treatment in this subset of cancers.

In addition to ATM, the checkpoint kinases Chk1 and Chk2 are critical for cell cycle checkpoint activation following induction of DSBs. There are several lines of evidence that suggest that the combination treatment of tumors with genotoxic agents and Chk1 or Chk2 inhibitors may have high therapeutic value. The first inhibitor of Chk1 and Chk2 was the staurosporine inhibitor UCN-01, treatment with this compound led to G2/M checkpoint defects in IR-treated p53-deficient tumor cells (28), suggesting that inhibition of the checkpoint kinases may preferentially sensitize p53 deficient tumor cells to radio- and chemotherapy. This finding stimulated interest in the development and testing of Chk1 and Chk2 inhibitors that may show antitumor properties when combined with other chemotherapeutics. One potential clinical challenge for the use of UCN-01 as a tumor treatment is the sensitization of normal tissues due to the broad spectrum of its targets. Increased myelosuppression was seen in phase I clinical trials of UCN01 with topotecan at lower doses than when topotecan was used alone (29, 30). With increasingly selective inhibitors and biomarkers it is likely that better therapeutic indexes can be achieved in clinical settings.

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Inactivation of p53 is a crucial event during the onset of tumorigenesis with approximately 50% of all human cancers containing somatic mutations in the p53 gene (36). A major
breakthrough in molecular-based therapy of cancer would be to restore the function of mutated p53 in cancer cells. Because the function of p53 is reduced in 50% of cancers, efforts to use it as a chemotherapeutic target have concentrated on agents that can reactivate p53 activity in tumors (reviewed in ref. 37). At present there are two main mechanisms of increasing p53 activity in tumors, the first mechanism involves restoring wild-type p53 function via a recombinant adenovirus encoding p53 (Advexin, phase I–III clinical trials; ref. 38; and Gendicine, approved for use in China and SCH 58500, phase I–II clinical trials; ref. 39). In addition, the tumor suppressor function of mutant p53 may be restored by the use of small compounds (CP-31398 and PRIMA-1) or short peptides (CDB3 and peptide 46; ref. 37). Although preliminary studies were encouraging, insufficient bio-availability of the small compounds have prevented their development as pharmacological therapeutics. Furthermore, the exact mechanism of rescue by these small compounds is unknown and the restricted range of p53 mutants that they can rescue limits their therapeutic potential.

The second mechanism of action involves the stabilization of p53 via small molecules that target the interaction between p53 and MDM2 (the E3 ligase responsible for ubiquitin-independent degradation of p53). These include nutlins, benzodiazepines, RITA, spiro-oxindoles, and quinolinols, all of which are at the preclinical development stages (37). Overexpression of MDM2 is also a hallmark of the mis-regulation of the p53 pathway in human cancers (40). MDM2 is a negative regulator of p53, therefore overexpression leads to the inhibition of p53 activity by altering the subcellular localization of p53, which in turn decreases its stability. Thus, in tumors that retain wild-type p53, inhibition of MDM2 can be used to reactivate p53 activity. Table 1 provides further information on compounds and clinical trials involving compounds targeting p53.

The MRN complex is a key component of DSB repair pathways and is also required for cell cycle checkpoint activation. Given the radiosensitive human genomic instability syndromes (discussed above) that arise from deficiencies in the Mre11 and NBS1 components of the MRN complex, this complex is an attractive target for anticancer treatments (2, 41). In the laboratory the use of a small peptide containing the evolutionary conserved region of NBS1, which binds to ATM, was found to disrupt the interaction between NBS1 and ATM (42).

### Table 1. Cancer therapies targeting components of damage response pathway

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class</th>
<th>Phase</th>
<th>Combination</th>
<th>Tumor type</th>
<th>Status</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCN-01</td>
<td>Chk1 and Chk2 inhibitor</td>
<td>I/II</td>
<td>Irinotecan, cisplatin, topotecan</td>
<td>Breast, gastric, head and neck, non–small cell lung, lung, small cell, ovarian, pancreatic, prostate, bladder, melanoma, thyroid, lung</td>
<td>Ongoing</td>
<td>(64)</td>
</tr>
<tr>
<td>AZD-7762</td>
<td>Chk1 and Chk2 inhibitor</td>
<td>I</td>
<td>Irinotecan, gemcitabine</td>
<td>Solid tumors</td>
<td>Ongoing</td>
<td>(31)</td>
</tr>
<tr>
<td>XL884</td>
<td>Chk1 and Chk2 inhibitor</td>
<td>I</td>
<td>Gemcitabine</td>
<td>Chronic lymphocytic leukemia</td>
<td>Terminated</td>
<td>(31)</td>
</tr>
<tr>
<td>PF-00477736</td>
<td>Chk1 and Chk2 inhibitor</td>
<td>I</td>
<td>Gemcitabine</td>
<td>Solid tumors</td>
<td>Ongoing</td>
<td>(31)</td>
</tr>
<tr>
<td>Advexin</td>
<td>Recombinant adenovirus encoding p53</td>
<td>I–III</td>
<td>—</td>
<td>Head and neck, breast, esophageal, prostate, ovarian, bladder, bronchoalveolar, glioblastoma</td>
<td>Ongoing</td>
<td>(38)</td>
</tr>
<tr>
<td>Gendicine</td>
<td>Recombinant adenovirus encoding p53</td>
<td>Approved for use in China</td>
<td>—</td>
<td>Head and neck</td>
<td>—</td>
<td>(39)</td>
</tr>
<tr>
<td>SCH 58500</td>
<td>Recombinant adenovirus encoding p53</td>
<td>I–II</td>
<td>—</td>
<td>Ovarian, lung, bladder, liver</td>
<td>Ongoing</td>
<td>(39)</td>
</tr>
<tr>
<td>CP-31398, PRIMA-1, CDB3, Nutlins, benzodiazepines, RITA, Spiro-oxindoles, and quinolinols</td>
<td>Mutant p53 reactivator MDM2-p53 interaction inhibitor</td>
<td>Preclinical</td>
<td>—</td>
<td>—</td>
<td>(65–67)</td>
<td></td>
</tr>
<tr>
<td>BSI-201</td>
<td>PARP inhibitor</td>
<td>I–III</td>
<td>—</td>
<td>Glioma, epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>Ongoing</td>
<td>(57, 73)</td>
</tr>
<tr>
<td>AG-014699 Olaparib (AZD2281)</td>
<td>PARP inhibitor</td>
<td>II</td>
<td>—</td>
<td>Breast, ovarian BRCA1- and BRCA2-mutated breast and ovarian cancer</td>
<td>Ongoing</td>
<td>(57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I–II</td>
<td>—</td>
<td>—</td>
<td>Ongoing</td>
<td>(57, 61–63)</td>
</tr>
</tbody>
</table>
addition, this peptide also prevented DNA damage signaling and radiosensitized cells, suggesting that targeting the NBS1: ATM interaction may be a successful target for anticancer drugs. A recent study used a forward genetic screen to identify a specific inhibitor of the MRN complex, designated as Mirin. Mirin inhibits MRN-dependent ATM activation and abolishes the endonuclease activity of Mre11. The consequence of the Mirin-dependent MRN inhibition is the prevention of G2/M checkpoint activation and HR repair (43). There is still more work to be done on demonstration of its antitumor activity in xenograft models.

Rad51 is required to protect cells from tumor development via its DSB repair capacity, however, once tumors form, Rad51 can also promote the resistance of tumors to chemotherapy (44, 45). Depleting the levels of Rad51 via antisense RNA or RNAi has been shown to sensitize tumor cells to chemotherapy agents, such as cisplatin (46–48). The above studies implicate Rad51 as a potential target for antitumor drugs. A recent study used short peptides encompassing the Rad51 interacting domain of the BRCA2 protein to examine their inhibitory effect on Rad51 activity (48). A peptide of 28 amino acids was found to bind Rad51, prevent its DNA binding activity, and therefore specifically inhibit the formation of the Rad51 nuclear foci and therefore the completion of HR in human cells. Although thus far this peptide has only been used as a research tool, further study of this peptide or peptidomimics may form the basis for antitumor drugs targeting Rad51 and the HR pathway in tumors.

The single-stranded DNA binding (SSB) proteins play essential roles in the repair of many types of DNA damage including DSBs. As well as being involved in the repair of DNA damage, SSBS are also central to other processes in which ssDNA is exposed, such as DNA replication. Until recently it was believed that RPA was the exclusive SSB involved in DNA repair in humans, however, two simple SSBS have been now identified, hSSB1 and hSSB2, with a crucial role in DNA repair (9, 49). The cellular function of RPA and hSSB1 in DNA replication and DNA damage repair and signaling makes them a very attractive cancer therapeutic target. Indeed, one study sought to identify potential chemicals that would inhibit the interaction of RPA with DNA. Using a fluorescent-based reporter assay they identified a number of inhibitory chemicals with possible therapeutic potential (50). hSSB1 is also the center of a current drug discovery program that aims to find potential therapeutic inhibitors of its function.

In addition to targeting cell cycle checkpoint activation and HR, there is also evidence that targeting the NHEJ pathway may also be an effective cancer treatment. Cells deficient in Ku70/80 or the catalytic subunit of DNA-PK (DNA-PKcs) are sensitive to DSBs induced by IR or chemotherapeutic agents (51, 52), suggesting that DNA-PK may constitute a good target for chemotherapy. In addition DNA-PK is upregulated in some cancers, implicating it as a factor required for tumor growth and survival. Indeed upregulation of DNA-PK activity was shown to impair apoptosis in B-cell chronic lymphocytic leukemia (53). Preliminary investigations into inhibition of DNA-PK used the broad-spectrum PIKK inhibitors wortmannin and LY294002 (54). These nonselective inhibitors were shown to sensitize tumor cells to chemotherapeutic agents and were used as a basis to develop a more specific DNA-PK inhibitor. Treatment with a flavonoid-based DNA-PK inhibitor IC87361 led to tumor radiosensitization in vitro and in vivo without causing toxicity (55). In subsequent studies a highly potent and selective DNA-PK inhibitor NU7441 with an IC50 of 13nM was identified (56). The use of this agent led to radiosensitivity and chemosensitivity of tumor cell lines and in xenograft models in preclinical trials. A number of other agents targeting DNA-PK are currently in clinical trials (57).

Recently, the fact that HR is essential for DNA repair in the absence of Poly (ADP-ribose) polymerase (PARP-1) has been exploited for cancer treatment. PARP-1 is a member of the base excision repair pathway that repairs ssDNA breaks. Inhibition of PARP-1 leads to accumulation of single-strand breaks, which are converted to DSBs during replication. The inhibition of PARP has been shown to be synthetically lethal with loss of BRCA1 and BRCA2 (58, 59). As a proof of concept, exposure of BRCA2-deficient murine tumors to PARP-1 inhibitors (KU-0059436/AZD2281) resulted in a profound decrease in tumor growth and survival (60). In addition, this inhibitor has shown a low level of toxicity and was found to stabilize or regress chemotherapy-refractory ovarian, breast, or prostate cancers with BRCA1 or BRCA2 mutations, and no activity was seen outside BRCA1- and BRCA2-defective tumors. In addition, a recent phase 1 clinical trial also found that AZD2281 inhibited PARP-1 and exhibited antitumor activity in ovarian, breast, or prostate cancers with BRCA1 or BRCA2 mutations (61–63). A number of PARP-1 inhibitors are currently in clinical trials as monotherapy for BRCA1- and BRCA2-defective breast and ovarian cancers (see Table 1 for further detail of specific inhibitors; ref. 57). The recent clinical finding validates synthetic lethality as a new concept in cancer drug development, and encourages the characterization and targeting of other synthetic lethality relationships in DNA damage response and repair pathways.

Conclusions

As our understanding of the mechanism and biochemical details of the DNA damage response increases, the potential ways to manipulate this pathway for the development of novel therapeutics will emerge and will have an enormous impact on future medical science. Success will rely on the availability of biomarkers to detect patients with particular checkpoint or DNA repair defects including defects in p53, HR, or FA pathways to stratify patients that should be trialed with a novel, targeted therapy.

It is likely that the response to cancer therapeutics will also become more predictable, with the identification of tumor biomarkers, thus allowing for targeted, more efficient cancer treatments. Further examination of the therapeutic and oncogenic effects of checkpoint and repair inhibitors is warranted to identify the most appropriate targets. The importance of DSB signaling and repair pathways in chemotherapeutic radiosensitization of cancer cells in vitro has been well characterized, however, the correlation between the in vitro clinical response to chemotherapeutic and radiotherapy and disruption of the DSB response pathway remains to be elucidated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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