

DNA Damage and Repair in Translational Oncology: An Overview

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Abstract

Unknown to early investigators, DNA damage and repair has been a major focus of anticancer therapy from the beginning of clinical oncology. From the early days of using x-irradiation, to the development of nitrogen mustard analogs, to today's more sophisticated approaches, DNA damage and repair has strongly impacted our ability to successfully treat human malignancy. This area of basic, translational, and clinical science is very broad. The traditional focus of DNA damage and repair has been on diseases such as Xeroderma pigmentosum, and attempting to understand the basic molecular mechanisms of DNA repair processes. It is only recently that we have begun to appreciate how we might modulate these processes to improve our ability to advance cancer care. No fewer than 10 separate DNA repair processes are operative in higher organisms, and the total number of separable processes could be substantially higher. Some of our most useful clinical agents depend on causing DNA damage that is repaired by nucleotide excision repair. X-irradiation induces damage that is mostly repaired by base excision repair and double-strand break repair. We are now learning how to modulate select DNA repair pathways to benefit patients with breast cancer and other malignancies. *Clin Cancer Res*; 16(18); 4511–6. ©2010 AACR.

DNA damage and repair is a subject of enormous breadth and depth. We commonly underestimate the importance of DNA damage and repair in the successful treatment of cancer, and, in general, also underestimate the overall importance of DNA damage and repair in oncology. For example, the most widely used class of anticancer compounds is the platinum series of agents, cisplatin, carboplatin, and oxaliplatin (1, 2). One or more of these agents represents the cornerstone of the current standard of care in the vast majority of solid tumors, including lung cancer, head and neck cancers, upper and lower gastrointestinal malignancies, genitourinary malignancies, and solid tumors of childhood. Alkylating agents have long been the backbone of treatment regimens for lymphomas, and other hematologic malignancies. Radiation therapy is critically important to cure, in a large range of early stage diseases. Despite its importance, much less is written about DNA repair than many of the other common subcellular processes that govern cancer causation and cancer treatment.

DNA damage occurs in many forms, as a result of a range of many different types of exposures. Similarly, DNA repair is executed in a variety of ways; these processes

having evolved over many millions of years, with the earliest of versions seen in the most rudimentary unicellular life forms. At a minimum, most would agree that the following are distinct pathways of DNA repair that occur in higher organisms: nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), double-strand break repair (DSBR), direct reversal, translesion synthesis, homologous recombination, and nonhomologous end-joining.

In this issue of *Clinical Cancer Research*, we touch on several subtopics related to DNA damage and repair that may be of interest to the translational scientist. In the collection of articles presented, we have chosen a series of topics of immediate importance in a translational oncology context. In two articles, the authors discuss new classes of anticancer agents that are in various stages of clinical trials, including the poly-ADP ribose polymerase (PARP) inhibitors and other DNA damage–modulating agents (3, 4). In a third article, biomarkers of DNA repair are discussed (5). In a fourth, current knowledge about the epigenetic influences on the DSB–DNA repair process is discussed (6). A final article discusses the possible importance of tumor cell hypoxia as an influence on the effectiveness of DNA repair (7).

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A Summary of DNA Repair Pathways

One of the exciting aspects of the recent development and successful translation of PARP inhibitors to the clinic is the proof of concept that modulating DNA repair can achieve clinical benefit. Two concepts seem to have been validated. One is that patients who have germline

deficiency in the DNA repair protein BRCA1 have clinical sensitivity to inhibition of PARP by olaparib as a monotherapy, pushing accumulated DNA damage in the cell to double-strand DNA breaks (8, 9).

The second proof of concept was demonstrated activity of the combination of gemcitabine and carboplatin with the PARP inhibitor BSI-201 (10). This strategy exploited inhibition of PARP, needed to repair DNA damage resulting from carboplatin and gemcitabine, to increase cell damage (10). The role of PARP inhibitors in clinical oncology is a theme running throughout this *CCR Focus* issue. Importantly, these studies that validate PARP as a therapeutic target also raise the question of whether the various other pathways of DNA repair might be exploited for clinical use.

A number of excellent reviews on the molecular processes of DNA damage and repair are available. For the interested reader, three highly recommended reviews are those of Hoeijmakers (11), Jackson and Bartek (12), and Clever and colleagues (13). Variation exists among DNA damage repair experts about the precise number of DNA repair pathways. For example, differences of opinion are seen in whether NER is one pathway, or two: global genomic repair and transcription-coupled repair. Similarly, the question arises about whether BER should be considered as one DNA repair pathway, or two: short patch repair, and long patch repair. The same applies to homologous recombination and nonhomologous end-joining, as subsets of DSBR. A list of DNA damage repair pathways and/or mechanisms, collated from the three reviews listed above, is given in Table 1. The summary below, although simplified, may serve as a starting point for increasing our understanding of this complex topic:

- NER executes the repair of DNA lesions induced by UV light, by polycyclic aromatic hydrocarbons, by heavy metals such as platinum and cadmium, and by other sources that form bulky DNA lesions that distort the DNA helix. The protein complex that executes the repair process consists of more than 16 distinct proteins, each of which has a distinct function. The complex is the home of the Xeroderma pigmentosum genes, *ERCC1*, and other genes associated with defined clinical syndromes of DNA repair deficiency. NER occurs either as global genomic repair, or transcription-coupled repair.
- BER executes the repair of apurinic and apyrimidinic sites within DNA, as well as simple alkylations. Apurinic sites and apyrimidinic sites are commonly caused by oxidative DNA damage, such as that resulting from normal mitochondrial processes. Other sources of oxidative damage may result in lesions repaired by BER. BER occurs in either of two forms: long patch repair or short patch repair.
- MMR restores DNA sequence integrity to mismatches in DNA base pairings, and in circumstances in which slipped intermediates in DNA base pairings occur. These types of changes in DNA tend to occur during DNA replication. MMR seems to be important in the

development of an important percentage of colorectal cancer cases, as well as other malignancies.

- DSBR occurs in response to x-irradiation, DNA torsional strain, homologous and nonhomologous recombination, and as an intermediate step in other types of DNA repair. The potential lethality of DSBs that are not repaired is unquestioned. However, it is also true that DSBs are a normal part of DNA physiology in the context of immune system function. Two subsets of repair in DSBR have been described, homologous recombination and nonhomologous end-joining. The development of immunoglobulin variability and specificity is a direct function of nonhomologous end-joining. Similarly, the normal cellular response to some viruses involves the efficient activity of homologous recombination.
- Direct reversal is very important in the cellular response to certain types of direct damage to DNA bases, such as O-6 alkyl guanine. Direct reversal is the cellular response when a single base is attacked and damaged, and this damaged base is directly repaired with little or no effect on surrounding DNA bases. This process is distinct from NER, BER, or MMR, in which surrounding DNA bases may be replaced as a function of the DNA repair process.
- Translesion synthesis is operational in those settings in which a damaged DNA base cannot be repaired, for whatever reason, and new DNA is faithfully synthesized in proper sequence in the face of that damaged DNA base. Stated simply, normal corrected DNA is synthesized over the DNA damage, which may, or may not, occur in the setting of template switching. Recent studies show that several specific DNA polymerases are critically important to this DNA repair process. This process may be of importance in the setting of several chemotherapy agents, such as cisplatin.

Table 1. DNA damage and repair pathways and/or mechanisms

NER
Global genomic repair
Transcription-coupled repair
BER
Short patch repair
Long patch repair
DSBR
Homologous recombination
Nonhomologous end-joining
MMR
Direct reversal
Translesional synthesis
Template switching
FANC pathway
ATM-mediated DNA damage repair signaling
ATR-mediated DNA damage repair signaling

- The Fanconi anemia (FANC) pathway is important in the repair of DNA interstrand cross-links, as may occur with chemotherapeutic alkylating agents. Ataxia telangiectasia mutated (ATM)-mediated signaling and ATM and Rad3-related (ATR)-mediated signaling are important in some repair settings for DNA single-strand breaks, and ssDNA abnormalities in the DNA.

If this stratification of DNA damage repair pathways is accepted, then the total number of different DNA repair pathways and/or mechanisms is 13. For most questions currently investigated in clinical oncology and translational oncology, the focus tends to be on NER, BER, MMR, DSB, and direct reversal.

The tradition that is observed by many DNA damage experts is to think of DNA repair in the context of the known associated diseases, such as Xeroderma pigmentosum. Such diseases are excellent examples of what can go wrong clinically in the absence of normal function of one or more DNA repair proteins. The goal of this review and this *CCR Focus* issue is to stimulate our thinking about DNA repair, as it might relate to translational and therapeutic applications in oncology. Posed in an alternative manner, are there more subtle DNA repair changes and/or modifications that have translational and clinical importance in the oncology setting?

The Need for Biomarkers

DNA damaging agents can be toxic to both tumor cells and normal tissues. It would, therefore, be useful if one could accurately assess who might benefit from such therapies, and who would not benefit. Using this approach, one could administer specific DNA damaging therapies only to those who would benefit; and, thereby, avoid toxicity in those who would be predicted to have no benefit. An accurate biomarker could be very useful in such a setting. This approach seems to have substantial value, for example, in the use of ERCC1 for gauging the effectiveness of cisplatin or carboplatin use in non-small cell lung cancer (14, 15). Another example is given by Pommier and colleagues, who discuss the development of an assay to infer the presence and magnitude of DNA damage based on foci composed of histone H2A phosphorylated at serine 139, termed gammaH2AX (5).

ERCC1 was first described by Hoeijmakers and colleagues in cross-complementation studies conducted in Chinese hamster ovary cells (16). Located on chromosome 19q, ERCC1 has sequence homology with *uvrA* and *uvrC*, and seems to carry out specific functions in NER, and in nonhomologous DSB (16–18). In fact, ERCC1 is the only protein that has functions in both of these DNA repair pathways.

Early *in vitro* studies suggested that ERCC1 mRNA and/or protein seemed to be directly related to the level of DNA repair activity in cultured cells (reviewed in ref. 19). Also, in a range of tumor types, ERCC1 levels of mRNA or protein seemed to be related to whether a patient's tumor would be

responsive to platinum-based chemotherapy, or not (19). High levels are associated with clinical resistance to therapy and adverse outcomes; low levels are associated with clinical sensitivity to therapy and favorable clinical outcomes. These laboratory and clinical observations are consistent with basic science observations that: (a) functional ERCC1 protein is necessary for NER to occur (11, 16); and (b) that NER is the pathway that repairs platinum–DNA adducts (15, 19, 20). Single nucleotide polymorphisms (SNP) in ERCC1 that are associated with reduced ERCC1 function are also associated with clinical tumor sensitivity and favorable clinical outcomes (21–23).

In non-small cell lung cancer, studies from a number of groups have consistently shown a strong relationship between high levels of ERCC1 mRNA and/or protein, and clinical resistance to platinum-based chemotherapy (14, 15, 24, 25). Also, a consistent relationship exists between low ERCC1 levels and favorable clinical outcomes. An early study considered to be crucial to this development was the International Adjuvant Lung Cancer Trial, published in 2006 (14, 15). Among 761 tumors assessed for ERCC1 protein expression by immunohistochemistry, 335 were positive and 426 were negative for detectable ERCC1 protein. Among patients with ERCC1-negative tumors, cisplatin-based chemotherapy was associated with a statistically significant improvement in survival, $P = 0.002$, as shown in Fig. 1. Among patients with ERCC1 positive tumors, no difference in survival was seen between those who received cisplatin-based therapy, versus those who did not, $P = 0.40$.

Multiple studies have confirmed the findings of that initial study (24, 25). The cumulative data for this relationship in NSCLC are sufficiently strong that this strategy has begun to be used in clinical decision making in this disease.

Recent data from prostate cancer (26), non-small cell lung cancer (27), and breast cancer (28), suggest that a related protein, XRCC1, may have prognostic significance for clinical response to x-irradiation, in a manner similar to ERCC1's potential role in chemotherapy response, discussed above. XRCC1 is a critical gene in BER, which plays an important role in the repair of some types of radiation-induced DNA damage (11–13).

Figg and colleagues studied XRCC1 in a cohort of 513 individuals, including patients with prostate cancer and normal controls (26). Among the individuals with prostate cancer were 284 who received radiotherapy. Within this subset of 284 patients, SNPs of XRCC1 and of ERCC1 were assessed and compared with clinical outcome after the x-irradiation. XRCC1 SNPs associated with reduced XRCC1 function were associated with a median survival of 11.75 years. Patients bearing XRCC1 SNPs associated with efficient function of the XRCC1 protein had a median survival of 6.21 years. This relationship strongly suggested the possibility that efficient BER was associated with prostate cancer that was more resistant to radiotherapy. ERCC1 showed no relationship with patient survival after radiation therapy, suggesting that NER played no role in this relationship.

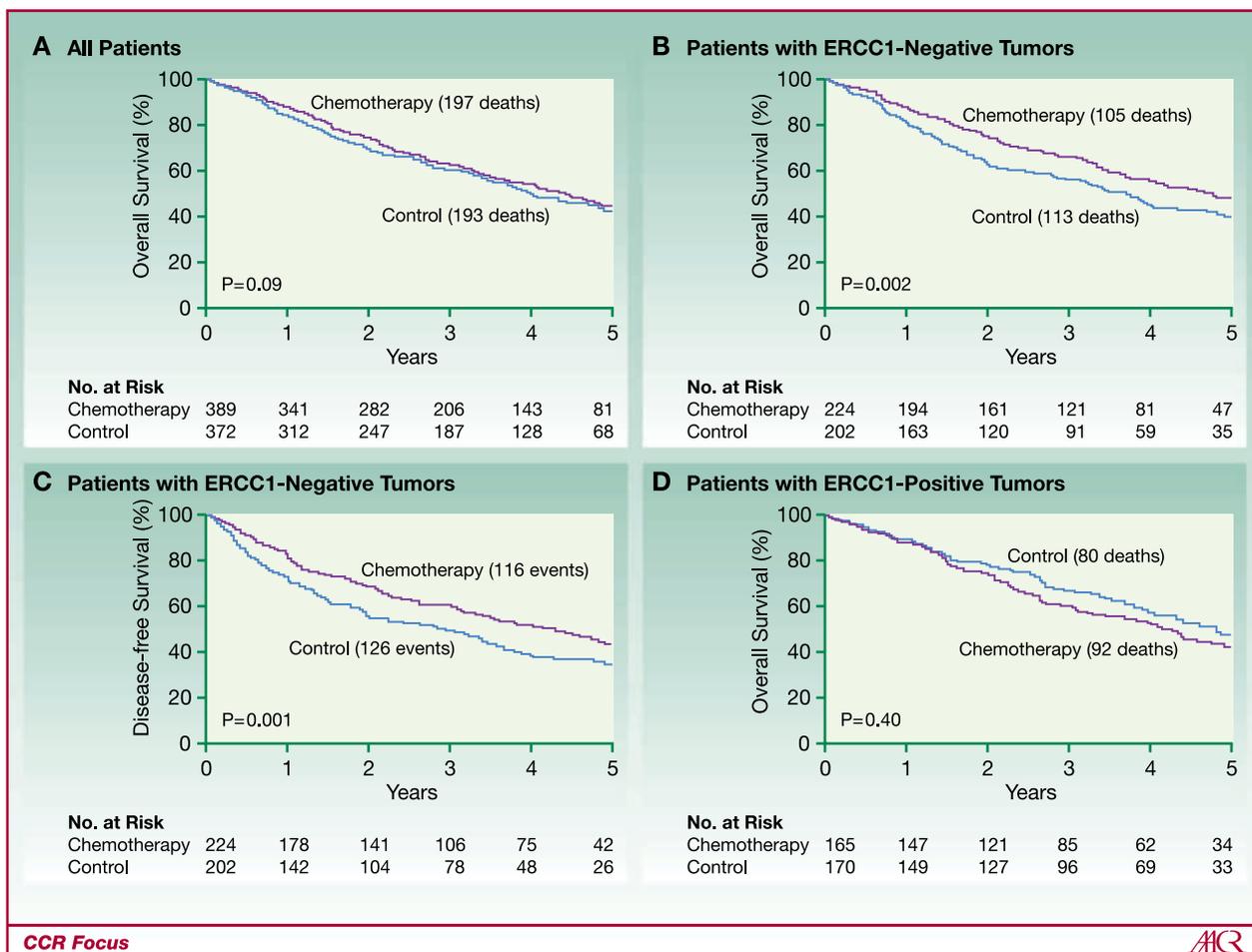


Fig. 1. Shown are the survival curves published by Olaussen and colleagues in the *New England Journal of Medicine* article cited in reference 14. These curves are Kaplan-Meier estimates of the probability of survival, as determined for: A, all patients; B, overall survival for patients with ERCC1-negative tumors; C, disease-free survival for patients with ERCC1-negative tumors; and D, overall survival for patients with ERCC1-positive tumors. As shown in B and C, patients with ERCC1-negative tumors showed improved survival when treated with cisplatin-based adjuvant chemotherapy. D shows that patients with ERCC1-positive tumors showed no differences in survival, whether or not they received cisplatin-based chemotherapy. These data were interpreted to show that patients with ERCC1-negative tumors will probably benefit from platinum-based chemotherapy; whereas patients with ERCC1-positive tumors will not. As discussed in the text, and specifically in references 24 and 25, a large number of subsequent studies in non-small cell lung cancer have confirmed these findings. Reproduced from Olaussen et al. (14). Copyright © 2006 Massachusetts Medical Society. All rights reserved.

These observations are also consistent with the thesis that NER has no role in the repair of DNA damage caused by x-irradiation; and, that BER is the clinically relevant DNA repair pathway for this type of DNA damage. Taken together, these data validate the importance of DNA repair pathways as a therapeutic target.

The Control of DNA Damage and Repair

An alternate strategy for study hypothesizes that effective anticancer therapy might result from strategies that reduce DNA repair capacity. As discussed by Côté and colleagues in this *CCR Focus* issue, a growing body of data suggests an important role for epigenetics in the control of DSB repair processes (6). A body of data also suggests an im-

portant contribution from transcriptional regulation, as discussed below.

The positive transcriptional regulator for ERCC1 is activator protein 1, or AP1 (29). AP1 is a heterodimer of c-jun and c-fos, and can be upregulated in response to activation of the stress-activated protein kinase (SAPK) pathway or the extracellular-related kinase (ERK) pathway (30, 31). AP1 can be downregulated by a number of pharmacologic maneuvers (32, 33), or by using a gene-based approach (34). The gene-based approach is executed by introducing a dominant negative to c-fos, with disruption of the hetero-dimerization of c-fos and c-jun. Thus, AP1 cannot be upregulated. In this setting, ERCC1 upregulation is blocked, and cells do not repair cisplatin-induced DNA damage (34).

Whatever approach is taken to disrupting or down-regulating AP1, the result is the inability of targeted cells to upregulate ERCC1, the consequent inability to repair cisplatin-induced DNA damage, and increased cytotoxicity from a defined cisplatin exposure. To date, this approach has not been pursued clinically.

The negative transcriptional regulator of ERCC1 is myeloid zinc finger protein 1 (MZF1; ref. 35). MZF1 is upregulated in those settings in which AP1 is downregulated; and, MZF1 is downregulated when AP1 is upregulated. The specific modulation of MZF1, and study the ERCC1 response to that modulation, has not been reported.

The AP1 effect on ERCC1 is accompanied by a parallel response of XRCC1 (36, 37). Whereas ERCC1 is an important marker for NER, XRCC1 is an important marker for BER. The two genes lie in close proximity to one another on chromosome 19q (38). When AP1 is disrupted or downregulated, ERCC1 and XRCC1 are blocked in concert. We have shown that AP1 has a binding site in the 5' untranslated region of the *XRCC1* gene, identical to the AP1-binding site demonstrated for ERCC1 and other genes involved in the NER–DNA repair complex (39).

Whether transcriptional regulation could be employed clinically to alter the ability of cells to repair following DNA damage is not known. All of the inhibitors in development to date have targeted proteins in the DNA repair pathways, rather than targeting regulation. Given the data showing ERCC1 impact on survival and the data showing efficacy of PARP inhibition in breast cancer suggesting that inhibition of DNA repair proteins sensitizes cancer cells to chemotherapy, we can infer that strategies to modify transcription of the DNA repair enzymes may have potential clinical utility.

One interesting approach that should be considered for study is the use of epigenetic therapy. Vorinostat has been shown to reduce function or level of DNA repair proteins, including RAD50, RAD51, Ku70, and Ku86, as one example (40).

CCR Focus on DNA Damage and Repair: From Bench to Clinic

Côté and colleagues note epigenetic changes in DNA that precede, facilitate, and conclude DNA repair (6). Signaling within the DNA repair process may be altered by ubiquitination, phosphorylation, methylation, or other processes. Histone acetylation is thought to confer an open chromatin state, allowing access to DNA repair proteins. Restoring the two-dimensional and three-dimensional status of the DNA requires specific epigenetic changes that follow DNA repair. Although the focus of the Côté report is on DSBR, the potential applicability of these observations to other DNA repair pathways is obvious.

Chan and Bristow, in this issue, discuss the concept of contextual synthetic lethality, as it may apply to DNA re-

pair (7). As discussed by these authors, tumor cell hypoxia has long been observed to be a roadblock to successful anti-cancer therapy. They discuss possible mechanisms by which tumor cell hypoxia may contribute to, more than simply altering the intracellular pharmacology of anticancer agents. They discuss the possibility that hypoxia may contribute to alterations in the intracellular molecular status of tumor cells, such that DNA repair is blocked; this could paradoxically increase the cytotoxicity of DNA damaging agents in some settings. This possibility deserves considerable further investigation.

PARP inhibition is an important avenue for the advancement of clinical therapy in breast cancer, and potentially a number of other malignancies. Annunziata and O'Shaughnessy explore possibilities in breast cancer in detail, and discuss PARP inhibition in the context of BRCA deficiency as well as in combination with DNA damaging agents (3). The development of appropriate biomarkers for this type of strategy is expertly reviewed by Pommier and colleagues (5). They focus on the question of early phase clinical trials, and how one might use this clinical context to develop and validate the use of biomarkers for PARP inhibition. A perspective on early phase drug development, as it relates to DNA damage and repair anticancer agents, is given by Plummer (4), who gives us a sense of the direction we might be collectively headed, in this exciting new area of clinical and translational research.

Summary Comments

In the mid-20th century, scientists working on mustard gas serendipitously discovered the potential use of agents to treat cancer. They did not initially recognize these drugs as DNA damaging agents, although the potential therapeutic value of x-irradiation was already under investigation. The study of DNA damage and repair, and its potential utility in the treatment of cancer, is not new. However, many new topics, ideas, and approaches need to be explored in this area.

Traditionally, DNA damage and repair have been considered in the context of rare diseases. More recently, we have come to understand that subtle changes in DNA repair may be major factors in cancer susceptibility, cancer causation, cancer recurrence, and response to anti-cancer therapy. In this issue of *Clinical Cancer Research*, we attempt to present a small measure of the very broad range of issues that we face, in our understanding of the potential applications of modulating DNA damage and repair.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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