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Review

Cancer Research

DNA Damage in Cancer Therapeutics: A Boon or a Curse?

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Abstract

Millions of DNA-damaging lesions occur every day in each cell of our bodies due to various stresses. The failure to detect and accurately repair these lesions can give rise to cells with high levels of endogenous DNA damage, deleterious mutations, or genomic aberrations. Such genomic instability can lead to the activation of specific signaling pathways, including the DNA damage response (DDR) pathway. Constitutive activation of DDR proteins has been observed in human tumor specimens from different cancer stages, including precancerous and metastatic cancers, although not in normal tissues. The tumor-suppressive role of DDR activity during the premalignant stage has been studied, and strong evidence is emerging for an oncogenic role for DDR proteins such as DNA-PK and CHK1 during the later stages of tumor development. However, the majority of current cancer therapies induce DNA damage, potentially exacerbating protumorigenic genomic instability and enabling the development of resistance. Therefore, elucidating the molecular basis of DNA damage–mediated genomic instability and its role in tumorigenesis is critical. Finally, I discuss the potential existence of distinct DNA damage thresholds at various stages of tumorigenesis and what the ramifications of such thresholds would be, including the ambiguous role of the DDR pathway in human cancers, therapy-induced malignancies, and enhanced therapies. *Cancer Res; 75(11); 2133–8. ©2015 AACR.*

Introduction

Human DNA is exposed to a variety of exogenous and endogenous genotoxic insults on a daily basis, which can result in DNA damage. There are multiple types of DNA damage as well as distinct but interrelated DNA repair mechanisms in humans. These include base modification [repaired by direct repair and base excision repair (BER)], base mismatch (repaired by mismatch repair), intrastrand crosslinks (ICL), and DNA–protein crosslinks [repaired by ICL repair and nucleotide excision repair (NER)], stalled replication forks [repaired by homologous recombination (HR), NER, and the Fanconi Anemia (FA) pathway], single-strand breaks (SSB; repaired by BER and HR) and double strand breaks [DSB; repaired by HR and non-homologous end-joining (NHEJ)]. These different DNA lesions and their corresponding repair mechanisms have been reviewed in detail by Curtin and colleagues (1).

DNA damage and the associated repair mechanisms play a crucial role in carcinogenesis, as most oncogenic alterations in humans (mutations, translocations, amplifications, deletions, and epigenetic modifications) are caused by the inefficient repair of damaged DNA. Of all DNA-damaging lesions, SSBs are the most common (roughly 10,000/day), and they are mainly the result of genotoxic insults from endogenous reactive oxygen species (ROS; ref. 2). SSBs are primarily repaired by BER, which is an extremely robust repair mechanism that protects cells from both endogenous and exogenous insults. In cases where such lesions are not repaired, particularly in proliferating cells, SSBs can lead to collapsed DNA replication forks, which in turn can give rise to DSBs, the most lethal of all DNA lesions (2). It has been estimated that in a normal human cell, 1% of SSBs are converted into approximately 50 endogenous DSBs per cell per cell cycle, which are primarily the result of ROS-induced DNA damage (1, 3). Notably, DSBs are not only difficult to repair, but are also directly damaging to the cell.

However, DSBs are also normal events that occur during cellular processes such as meiosis and somatic recombination. The majority of these DSBs are repaired by endogenous mechanisms such as HR and NHEJ, the latter being a more error-prone mechanism (1, 3). Interestingly, DSB repair is a process that is dependent on the phase of the cell cycle. Whereas NHEJ is active during all phases of the cell cycle, particularly during G_0, G_1, and early S phase, HR is most predominant during late S and G_2 phase (1, 3). Notably, NHEJ, which is error-prone, is thought to be the primary means of repair for therapeutically induced DSBs resulting from irradiation, radiomimetics, topoisomerase poisons, and ROS-inducing treatments (1, 4).

Therefore, a number of outcomes are possible for human cells with damaged DNA. (i) The damage is successfully detected and accurately repaired, and the cell is restored to normal functioning. (ii) The cell is unable to repair the DNA damage and activates the DNA damage response (DDR) pathway, which can cause senescence or death in the damaged cell; in case of radiotherapy, these cells generally die from mitotic catastrophe. (iii) The damaged DNA is misrepaired and the cell evades senescence and death, resulting in a population of cells that carries deleterious mutations or chromosomal aberrations with oncogenic potential (5, 6).

In fact, changes as small as a single base pair mutation in human DNA can be deleterious. These mutations are classified as driver mutations because they often perturb vital signaling

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cascades, potentially resulting in genomic instability, a hallmark of cancer. In cells, genomic instability results in the activation of various signaling pathways, including the DDR pathway. In humans, proteins in the DDR pathway can be functionally categorized into multiple classes, including DNA damage sensors, DNA damage mediators, downstream kinases, and DNA damage effectors that are directly involved in DNA repair.

Strikingly, the activation and increased expression of various DDR proteins and DNA adducts such as 8-hydroxy guanine (oxidative DNA damage) have been detected during all stages of cancer development, including premalignant and metastatic stages (7–9). Although the tumor-suppressive roles of these activated DDR proteins in early premalignant lesions are well established (8, 10), the molecular basis of their activation and function in tumor progression during later stages is still unclear. In this review, I first discuss the molecular mechanisms underlying constitutive DNA damage–mediated tumorigenesis, followed by a section on the importance and implications of DNA damage thresholds. Finally, I describe how the concept of distinct DNA damage thresholds can explain the various outcomes observed following DNA damage induction, and how it might affect cell fate in humans.

Emerging Evidence for the Role of Constitutive DNA Damage in Carcinogenesis

Although increased activity and/or expression of DDR proteins has been observed in human malignancies (7, 9, 11), targeting the DDR pathway has been mainly limited to the treatment of drug resistance (1) for two reasons. First, there are serious adverse effects and toxicity concerns stemming from the use of DDR-targeting drugs as single agents (1). Second, the molecular mechanisms of how constitutively increased DDR promotes cancer growth have only recently been uncovered (11, 12).

It has been suggested that deleterious mutations due to inefficient DNA damage repair are responsible for increased constitutive DNA damage in human malignancies (1). However, high-throughput sequencing as well as *in vitro* and *in vivo* studies have identified oncogene activation as one of the potential causes of DNA damage induction in cancer. Consistent with this idea, the activation of well-characterized oncogenes such as *MYC* and *KRAS* has been demonstrated to induce DNA damage via replication and oxidative stress mechanisms (13, 14). Furthermore, *MYC*-driven tumors are dependent on the activity of the DDR kinase checkpoint kinase 1 (*CHK1*) for their maintenance and growth (15, 16). These findings establish a tumor-promoting role for the bistable relationship between oncogenic signaling and DNA damage.

Of the various DDR proteins, PARP, CHK1, and DNA-dependent protein kinase catalytic subunit (DNA-PKc) have received significant attention from both industry and academia as potential anticancer targets, which is evident from the large number of small-molecule inhibitors targeting these proteins currently in clinical trials for use as combination or monotherapy agents against various solid tumors (1). The effectiveness of PARP inhibitors in BRCA1/2-defective tumors has been attributed to synthetic lethality. However, PARP inhibitors have also shown encouraging anticancer activity in clinical trials involving cancers with no germline *BRCA* mutations, such as high-grade serous ovarian cancer and triple-negative breast cancer (17), indicating a broader role for PARP in promoting the growth of these tumors.

Because of its role in the cell-cycle checkpoint, HR and its activation during the precancerous stages, *CHK1* is considered to be a tumor suppressor (8, 10). However, in recent years, an alternative paradigm focusing on the tumor-promoting role of *CHK1*, particularly in tumors driven by high replication and oxidative stress, has emerged (11, 16, 18, 19). Synthetic lethal cooperation between DNA damage induction and DDR protein inhibition has become the dominant paradigm for considering the nononcogene "addiction" of malignant cells to the activity of various DDR proteins such as CHK1 and DNA-PKc. In other words, tumor cells appear "addicted" to the chronic activity of these DDR proteins for their survival (11, 15, 16, 20). However, the molecular mechanisms underlying the chronically increased activity of these factors in unperturbed cancer cells, and their role in promoting the survival and growth of malignant cells are poorly understood.

We recently identified the oncogenes *CIP2A* and *MYC* as downstream effectors of the DDR proteins CHK1 and DNA-PKc (11). The *CIP2A* oncogene is an endogenous inhibitor of protein phosphatase 2A (PP2A) and is overexpressed in the majority of tumor types (21, 22). We demonstrated that chronic *CHK1* activity in unperturbed cancer cells promotes *CIP2A* transcription, thereby inhibiting PP2A tumor suppressor activity and establishing a link between DNA damage and PP2A inactivation (11). These results add to our understanding of constitutively active signaling circuits in cancer cells, and they provide an alternative strategy for impeding *CHK1*, *CIP2A*, and *MYC* activity in human malignancies (11). Consistent with these findings, *CHK1* overexpression is observed in many tumor types and is positively correlated with tumor grade and recurrence (18). Moreover, several recent studies have provided strong genetic evidence *in vivo* for the tumor-promoting role of *CHK1* (19, 20, 23). Tho and colleagues (19) demonstrated that genetic depletion of *CHK1*-suppressed tumor formation in a murine model of chemically induced skin tumorigenesis. At the same time, an independent study demonstrated the promotion of *Ras*-mediated malignant transformation in a transgenic mouse line carrying an extra *CHK1* allele (23). In addition, a large-scale loss-of-function screen of the protein kinome identified *CHK1* as a therapeutic target for neuroblastoma (20). Importantly, no homozygous loss-of-function mutations in *CHK1* have been reported in human cancers (18). These results indicate that the catalytic function of *CHK1* may be essential for the growth and survival of certain tumor cells. The role of *CHK1* in cancer therapy has been extensively covered in a recent review by Zhang and Hunter (18).

The DNA damage kinase DNA-PKc, a key component of the NHEJ pathway, is primarily involved in the repair of DSBs. Similar to *CHK1*, high expression and activity of *DNA-PKc* has been observed in colorectal cancers, gliomas, ALLs, CLLs, and non–small cell lung cancers and is correlated with tumor grade in these tumor types (12). Moreover, DNA-PKc stabilizes the MYC oncoprotein (11) and physically interacts with EGFR, which is frequently overexpressed in epithelial human tumors. A recent study revealed a positive-feedback loop between DNA-PKc and the androgen receptor (AR) in prostate cancer cells, providing a rationale for targeting DNA-PKc in AR-driven malignancies, particularly in advanced prostate cancer (24). In contrast with these findings, decreased DNA-PKc activity and expression has been reported in ovarian cancers, where this loss of expression was

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associated with tumor progression and metastasis (12). These paradoxical roles for DNA-PKc may be attributable to tissue specificity. However, similar antagonistic functions have been observed for many other DDR proteins, suggesting another more global phenomenon is at work.

DNA Damage Thresholds in Human Cancers

In eukaryotic organisms such as *Saccharomyces cerevisiae*, the thresholds of tolerable DNA damage (i.e., repaired without errors) and the mechanisms that regulate these thresholds have been elegantly delineated and defined. By contrast, relatively little is known concerning DNA damage thresholds and their ramifications in human cells, particularly in malignant cells. As previously stated, extrinsic and intrinsic factors cause damage to human DNA thousands of times each day. DNA damage is normally repaired by various endogenous repair mechanisms, resulting in the restoration of human DNA integrity with a relatively low driver mutation rate. This level of DNA damage in human cells, which can be managed effectively without an obvious phenotype, can be defined as the homeostatic threshold of DNA damage (level A in Fig. 1).

By contrast, in precancerous stage cells, increased DNA damage occurs, activating the DDR machinery. Activation of the DDR machinery during this stage augments tumor-suppressive mechanisms such as apoptosis, senescence, and the inhibition of malignant transformation (8). Uniquely, during the premalignant stage, the increased activity and expression of oncogenes is also observed (10). Whether tumor-suppressive or oncogenic processes dominate depends on the nature and location of subsequent mutations during this stage. According to the multistep carcinogenesis model of tumor progression, an oncogenic event at this point weakens the DDR-barrier and allows cells to escape DDR-mediated cell death or senescence. Then, the further accumulation of DNA damage stimulates various oncogenic signaling pathways to promote malignant transformation and uncontrolled growth (13, 25). This minimum threshold of DNA damage that is required to convert a premalignant lesion into a cancerous growth can be defined as the malignant threshold (level B in Fig. 1).

The next phase in the life cycle of a cancer cell is therapeutic intervention. Currently—together with surgery—chemotherapy and radiotherapy are the mainstays of treatment for most malignancies. Both chemo- and radiotherapy act by inducing DNA damage in cancer cells. This supraphysiologic level of DNA damage increases the likelihood of cell death due to mitotic catastrophe (in most cases), necrosis, apoptosis, or senescence (26). The minimum threshold of DNA damage that kills tumor

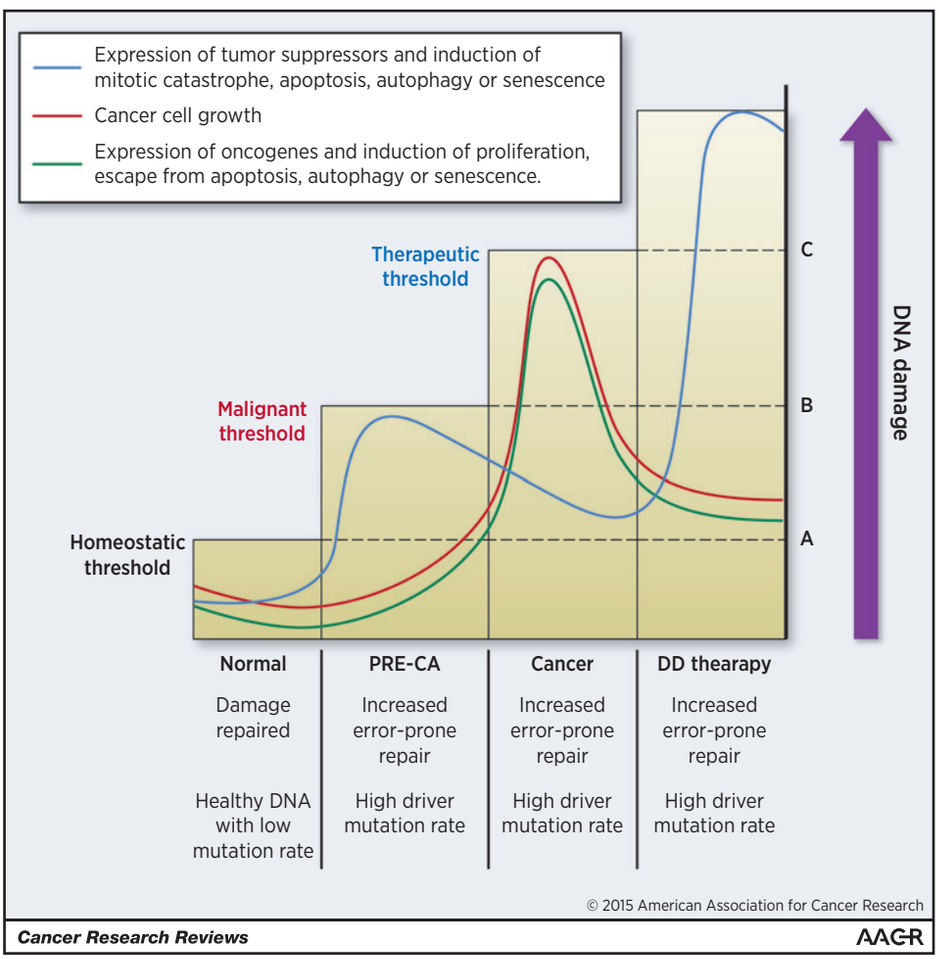

Figure 1.
Different thresholds (A, B, and C) of DNA damage at various stages of human cell transformation: normal, precancerous (Pre-CA), cancerous, and treatment with DNA damage–based therapies (DD therapy). The patterns of tumor-suppressive and oncogenic processes as well as the trends of error prone repair (misrepair) and driver mutation rates are also shown at each stage.

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cells directly or reactivates tumor-suppressive mechanisms in these cells can be defined as the therapeutic threshold (level C in Fig. 1).

Ramifications of Distinct DNA Damage Thresholds in Human Cancers

Advances in early detection methodologies, anticancer therapeutics (mainly chemo- and radiotherapy) and palliative care have increased the life spans of cancer patients over recent decades. However, these treatments have also increased the incidence of second malignant neoplasms (SMN; ref. 27). Approximately 17% to 19% of cancers diagnosed today have a previous history of a primary malignancy (27). The general risk of developing SMNs is thought to be higher in survivors of childhood cancers than adult cancers. This phenomenon could simply be due to the generally good prognoses of childhood cancers, which would allow for longer periods over which these therapies might be active. A study on adult cancer survivors attributed about 10% of second cancers to radiotherapy alone (28). Therefore, the overall incidence risk of second cancers in adult cancer survivors might be expected to be a slightly higher, particularly if one considers the contribution of chemotherapy, inadequate sample sizes, the lack of systematic long-term follow-up studies, and the probability of surviving the first cancer. Whereas primary cancer therapies and genetic make-up are major risk factors for SMNs in childhood cancer survivors, environment, and lifestyle choices may also play significant roles in adult cancer survivors (27). This makes studies on childhood cancer survivors more valuable in providing molecular insights into the role of primary cancer treatments in therapy-induced malignancies (TiM).

Radiotherapy can result in different types of cancers, and the risk is directly proportional to the dose and duration of treatment (29). Notably, in most cases, tumors resulting from radiation occur 10 years post-exposure, and this lag may reflect the time required for the accumulation of deleterious mutations (genotype) due to clonal selection and tumor manifestation (phenotype). These malignancies frequently develop within the areas exposed to radiation. For example, patients receiving radiation in the neck region have a higher risk of developing thyroid cancers, and those receiving cranial radiation have a higher risk of developing brain tumors, particularly when exposed at a younger age (29). Ironically, radiation has been proposed as both a risk factor and a treatment modality for malignancies of the central nervous system (29).

Chemotherapy has long been associated with tumorigenesis, particularly blood malignancies. Myeloid disorders such as AML and MDS have been linked to various cytotoxic anticancer drugs, and chemotherapy is considered to be a greater risk factor than radiotherapy in therapy-related myeloid malignancies. Accordingly, the latency period for chemotherapy-induced blood disorders ranges from one to 6 years after treatment (29). Chemotherapeutic drugs such as alkylating agents (e.g., cyclophosphamide, cisplatin, and busulfan), DNA topoisomerase inhibitors (e.g., etoposide and mitoxantrone), and anthracyclines, which act by inducing DNA damage in cells, are all associated with a higher incidence of myeloid neoplasms. Interestingly, these drugs, as well as azacitidine, a DNA methylation inhibitor commonly used to treat MDS patients, can induce genetic rearrangements (29, 30). Strikingly, these chemotherapy-induced myeloproliferative disorders are generally more resistant and have a worse prognosis than other cancers (29).

The concept of different DNA damage thresholds within a cell provides a plausible explanation for the occurrence of TiMs. Namely, the levels of DNA damage found in normal, healthy cells induced by chemo- or radiotherapy may breach the homeostatic threshold (level A in Fig. 1), and perhaps even the malignant threshold (level B in Fig. 1), resulting in transformation followed by the occurrence of TiMs (29).

The notion of different DNA damage thresholds is also consistent with the duality of the functions of DDR proteins such as DNA-PKc and CHK1. DDR activity is higher in advanced tumor stages, but impedes tumor progression in the precancerous stage. The paradoxical function of *MYC* in DDR and tumor progression can also be explained by this concept. Although the tumor-suppressive role of *MYC*-induced DDR during the early precancerous stage is well defined, its oncogenic function in the latter stages of cancer has been attributed to *MYC*-mediated *CHK1* regulation, which in turn modulates replication stress in transformed cancer cells (31). However, *MYC* and other oncogenes, such as *RAS*, also increase oxidative DNA damage (13, 14). Although, in principle, this induced DNA damage could stimulate the various tumor-suppressive pathways to restrict tumor progression, the opposite effect is observed (13). This disparity could be attributed to *MYC*-mediated DNA damage above the homeostatic level but below the malignant threshold during the precancerous stage, but which surpasses the malignant threshold and facilitates tumor progression during full-blown cancer. Molecular evidence supporting this hypothesis can be found in studies by our group as well as others.

In addition to enhancing our understanding of various aspects of cancer cell biology, the concept of distinct DNA damage thresholds could be useful for developing alternative therapeutic strategies for the treatment of human malignancies and overcoming drug resistance. For example, ROS- or oxidative damage-inducing drugs might be combined with antioxidant inhibitors to provide a microenvironment in which DNA damage is induced and maintained above the therapeutic threshold to more effectively target tumors.

Future Perspective

Although chemotherapy and radiotherapy, together with surgery, are the most effective and widely used anticancer modalities, the molecular consequences of their use require further elucidation. As more data on the molecular changes induced by DNA damage resulting from chemo- and radiotherapy emerge, quantitatively defining various DNA damage thresholds and accurately measuring total endogenous DNA damage will be instrumental in validating these hypotheses.

Many surrogate markers for DNA damage have been identified that can be used to assess the kinetics of DNA damage in cells. Of these markers, phosphorylated γH2A.X is one of the most widely used. Although γH2A.X is a very sensitive marker and can be used to measure DNA damage at the single-cell level, it does have significant limitations. First, this molecule preferentially marks actively transcribing euchromatic regions and does not mark the heterochromatin DSBs (5). Interestingly, heterochromatic DSBs have been shown to be repaired with slower kinetics and with less efficiency than euchromatic DSBs, rendering them far more damaging (5). Second, γH2A.X foci are also found in normal cells,

making the timing of the assay a crucial factor when measuring DNA damage, particularly when assessing DDR after therapy (32). Finally, γH2A.X does not recognize oxidative DNA damage as effectively as irradiation-induced DNA damage (32). Therefore, it will be necessary to combine multiple methods to accurately estimate cellular DNA damage. In addition, the identification of novel, sensitive, pan-DNA damage markers will be required, as the ramifications of incorrectly assessing DNA damage can be immense. For example, even a single cell with DNA damage over the malignant threshold could generate several clones, perhaps resulting in more aggressive and resistant tumors. In addition, it will be interesting to determine the link between heterochromatin-related DNA damage and tumor progression.

As nearly one fifth of cancers diagnosed today are found in cancer survivors (27), molecular insights into the etiology of SMNs are of immense clinical and social significance. Notably, the occurrence of SMNs in certain cancer patients treated with DNA damage-inducing therapies could be explained, at least in part, by the proposed concept of distinct DNA damage thresholds during cancer development and progression. Moreover, a recent study using mathematical modeling suggested that stochastic mutations due to perturbation in DNA replication are the major etiologic factor in human cancers (33). As both irradiation and chemotherapy are known to cause random mutations, it can be hypothesized, based on the above model, that these modalities increase the incidence of TiMs by simply increasing background mutations. Finally, the exact contributions from different primary cancer therapies, as well as from environmental effects and genetic make-up, toward the risk of developing SMNs, particularly in adult cancer survivors, need to be determined.

The advantages of using DNA-damaging therapies in patients must always be weighed against the risks of developing TiMs. Considering the proposed concept of distinct DNA damage thresholds, treatment strategies that balance the inevitable deleterious effects, while also providing effective anticancer therapies, might be developed. Finally, the stratification of patients based on their genetic make-up could further lead to more effective, less toxic, and safer cancer therapies.

Disclosure of Potential Conflicts of Interest

A. Khanna has ownership interest (including patents) in CIP2A as pharmacodynamic marker for *CHK1* and *DNA-PKc*-based therapies.

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