Human Nuclease/Helicase DNA2 Alleviates Replication Stress by Promoting DNA End Resection

Guang Peng1, Hui Dai2, Wei Zhang1, Hui-Ju Hsieh1, Mei-Ren Pan2, Yun-Yong Park2, Robert Yu-Lin Tsi4, Isabelle Bedrosian3, Ju-Seog Lee2, Grzegorz Ira5, and Shiaw-Yih Lin2

Abstract

In precancerous and cancerous lesions, excessive growth signals resulting from activation of oncogenes or loss of tumor suppressor genes lead to intensive replication stress, which is recognized by a high level of replication-associated DNA double-strand breaks (DSB). However, the molecular mechanism by which cells alleviate excessive replication stress remains unclear. In this study, we report that the human nuclease/helicase DNA2 facilitates homologous recombination to repair replication-associated DNA DSBs, thereby providing cells with survival advantages under conditions of replication stress. The nuclease activity of DNA2 was required for DSB end resection, which allowed subsequent recruitment of RPA and RAD51 to repair DSBs and restart replication. More importantly, DNA2 expression was significantly increased in human cancers and its expression correlated with patient outcome. Our findings therefore indicate that enhanced activity of DSB resection likely constitutes one mechanism whereby precancerous and cancerous cells might alleviate replication stress. Cancer Res; 1–12.

Introduction

Tumorigenesis is a multistep process by which normal cells successively acquire genetic alterations (1). Analyses of human tumors have shown that the presence of DNA damage, particularly DNA double-strand breaks (DSB), distinguishes precancerous lesions and cancer from normal tissues (2,3). Recent studies have indicated that oncogene-induced replication stress underlies DSB formation (4,5). Specifically, activation of oncogenes provides cells with sustained proliferative signaling and leads to inappropriate DNA replication, which results in fork collapse and DSBs (6,7).

There are 2 pathways for repairing DSBs: homologous recombination (HR) and nonhomologous end-joining (NHEJ; ref. 8). NHEJ involves direct ligation of broken ends and primarily occurs in the G1 phase of the cell cycle. HR is considered to be more error-free repair mechanism that copies sequences from the homologous template to repair damaged DNA. It predominantly occurs in the S- and G2 phases, when preferable template, sister chromatids, are available. Thereby, HR is a key pathway for repairing stalled and collapsed replication forks that occur spontaneously or are induced by topoisomerase 1 inhibitors such as camptothecin or polymerases inhibitors such as aphidicolin (9). Repair of chromosomal breaks by HR is initiated by resection of the 5’ strands that generates 3’ ssDNA tails at DSB ends (10,11). Resection allows loading of single-strand–binding protein RPA that is further replaced by key enzyme in HR, strand exchange protein RAD51 with the help of BRCA2 (12–14). RAD51 mediates homology search and strand invasion at template sister chromatid, which is followed by DNA synthesis and resolution of recombination intermediate that restores replication fork. Depletion of RAD51 leads to accumulation of unrepaired DSBs and cells death showing the importance of HR for repair of spontaneous DNA breaks occurring during replication (15).

Continuous formation of DSBs induced by replication stress activates DNA damage response (DDR), which induces senescence or apoptosis and thus prevents precancerous lesions from progressing to malignant lesions (6,7). Impairment of DDR (e.g., through loss of expression of signaling kinases ATM or CHK2) can lead to a breach of this anti-cancer barrier and tumor progression (4,5). However, it remains unclear that how precancerous and cancerous cells could cope with increased replication-associated DSBs and maintain their hyperactive DNA replication status.

In this study, we used a proteomic approach to investigate protein components preferentially associated with replication forks in the presence of oncogene activation. Here, we report that human nuclease/helicase DNA2 is overexpressed in a variety of cancers and it plays an important role in alleviating...
replication stress likely by promoting DNA end resection and HR repair of replication-associated DSBs.

Materials and Methods

Cell culture

U2OS and MCF10A cells were purchased from American Type Culture Collection (ATCC). U2OS cells were maintained in McCoy 5A medium supplemented with 10% FBS. MCF10A cells were cultured in mammary epithelial growth medium containing insulin, hydrocortisone, EGF, and bovine pituitary extract purchased from Clonetics. MCF7 cells were maintained in Dulbecco’s Modified Eagle’s Media (DMEM; Cellgro) with 10% FBS. Cell lines were validated by short tandem repeat (STR) DNA fingerprinting using the AmpFISTR Identifiler Kit according to manufacturers’ instructions (Applied Biosystems catalogue no. 4322288). The STR profiles were compared with known ATCC fingerprints, with the Cell Line Integrated Molecular Authentication database (CLIMA) version 0.1.200808 (Nucleic Acids Research 37:D925-D932 PMCID: PMC2686526), and with the MD Anderson fingerprint database. The STR profiles matched known DNA fingerprints or were unique. MCF10A cells with stable cyclin E expression were generated by transfection with pcDNA3.1-cyclin E construct and maintained in the presence of 100 μg/mL G418. A series of pancreatic cell lines (HPDE, PD90, PD78, PD77, and PD74) representing RAS-mediated pancreatic cancer development were kindly provided by Dr. Michel J. Quellette (University of Nebraska Medical Center, Omaha, NE). Cells were maintained as previously described (16).

Antibodies, immunoprecipitation, chromatin fractionation, and Western blot analysis

Antibodies used in the experiments include DNA2, H2AX, and rat anti-BrdU antibodies (Abcam); γ-H2AX (Upstate Biotechnology); RPAP34 (Neomarkers); p-RPAP34 (Bethyl Laboratories); Chk1, p-Chk1 (Ser345), and p-p53 (Cell Signaling); ORC2, PCNA, DNA polymerase δ, RFC2, RFC1, MCM2, and p21 (Santa Cruz Biotechnology); and Rad51 (Ab-1), mouse anti-BrdU, and p53 antibodies (Calbiochem). The immunoprecipitation with anti-Flag affinity beads was done in U2OS cells transiently transfected with Flag-tagged plasmids. Forty-eight hours later, whole-cell extracts were prepared with radioimmunoprecipitation assay (RIPA) buffer and immunoprecipitated with anti-Flag M2 affinity gel (Sigma) overnight. Bead-bound immunocomplexes were eluted with 3x FLAG peptide (Sigma) and subjected to SDS-PAGE. For reciprocal immunoprecipitation, whole-cell extracts were prepared in RIPA buffer as indicated above and precleared with protein A/G plus-agarose beads (Santa Cruz). Then, cellular extracts were subjected to incubation with antibodies against proliferating cell nuclear antigen (PCNA) and DNA polymerase δ (2 μg/mg of cell lysis) overnight and then incubated with protein A/G agarose beads for 4 hours at 4°C. The immunocomplex was eluted in loading buffer by boiling at 95°C for 5 minutes. The preparation of chromatin fractions and Western blot analysis, including the conditions for RPA analysis, were as previously described (17).

Statistical analysis

All statistical analysis was done using one-tailed Student t test. Additional methods are included in Supplementary Materials.

Results

DNA2 forms a complex with replication factors and prevents accumulation of replication-associated DSBs

On the basis of previous findings that the activation of oncogenic RAS causes replication stress and replication-associated DSBs, we selected the MCF10A and MCF10AT cell lines for proteomic analysis (4, 5, 18). MCF10A cells are immortalized normal breast epithelial cells. MCF10AT cells are derived from MCF10A cells by forced expression of oncogenic H-RAS. MCF10A cells do not grow in immunocompromised mice. In contrast, MCF10AT cells form the lesions that resemble the progression of breast cancer. Thus, these cell lines provided us with a model system to study the genetic alterations promoting carcinogenesis initiated by oncogene activation.

Replication forks are composed of many proteins. PCNA, DNA polymerase processivity factor, encircles DNA and orchestrates replication-linked processes by recruiting crucial players to the replication fork (19). Thereby, we used PCNA as our bait to isolate replication factor–associated protein complexes. Among many known proteins involved in DNA replication including RFC factors and MCM proteins, we found that DNA2 had higher abundance in MCF10AT cells than in MCF10A cells (Fig. 1A). We then conducted immunoprecipitation analysis to confirm DNA2 as a component of replication factor–associated protein complex (Fig. 1B; Supplementary Fig. S1A). This result is consistent with previous studies in yeast and Xenopus showing the involvement of DNA2 helicase/nuclease in DNA replication and repair (20, 21).

In humans, DNA2 is localized in both mitochondria and nuclei (22, 23). While the mitochondrial function of DNA2 was well-documented, its nuclear functions remain unknown. We found that DNA2 depletion impaired both the number of cells with active metabolic activity and cell survival (Fig. 1C and D). By neutral comet assay, we observed that DNA2-knockdown cells had a significantly higher proportion of cells with comet tails (Fig. 1D; Supplementary Fig. S1B), suggesting that DNA2 is required to prevent accumulation of endogenous DSBs.

We next examined whether DSBs present in DNA2-deficient cells were formed in cells with ongoing replication. γ-H2AX is a marker of DSBs (24). Bromodeoxyuridine (BrdUrd) incorporation represents actively replicating cells. We found that DNA2-deficient cells had a significantly higher proportion of cells with γ-H2AX staining and 60% of these cells also showed BrdUrd incorporation (Fig. 1E), which was significantly higher than that expected from a normal replication process (25). To further confirm that DNA2-knockdown induced replication-dependent DSBs, we showed that inhibition of replication by aphidicolin significantly decreased the number of cells with positive γ-H2AX staining (Supplementary Fig. S1C). In addition, analysis of metaphase spreads showed that DNA2-deficient cells were significantly more likely to exhibit chromosomal breakage (Fig. 1F). These findings supported an
important role of DNA2 in regulating accumulation of replication-associated DSBs and chromosomal stability.

**DNA2 accumulates at restarted replication forks and promotes HR repair**

To confirm the role of DNA2 in response to replication-associated DSBs, we pulse-labeled newly synthesized DNA with a thymidine analogue, chlorodeoxyuridine (CIdU). We conducted immunoprecipitation with antibody against CIdU to detect the protein complexes associated with newly synthesized DNA. Interestingly, we observed that the association of DNA2 with replication forks was indeed enhanced in the presence of camptothecin, which causes replication-associated DSBs (Fig. 2A). In addition, we found that DNA2-depleted cells were more sensitive to topoisomerase inhibitors generating replication-associated DSBs, camptothecin and
etoposide (Fig. 2B). Together, these data suggested that DNA2 accumulates at replication forks and plays a functional role in response to replication-associated DSBs.

Several studies implicated yeast and *Xenopus* DNA2 in the initial step of HR, resection of DSBs (26–30). Also, purified human DNA2 nuclease promotes DSB end resection (31). These reports, together with our observation, led us to hypothesize that DNA2 may prevent the accumulation of replication-associated DSBs by promoting HR repair. We first examined ssDNA formation at DSBs in DNA2-depleted cells. After cells were labeled with BrdUrd, we stained nondenatured BrdUrd, which is located only at ssDNA (32, 33). We found that reduced camptothecin triggered ssDNA formation in DNA2-depleted cells (Fig. 2C), suggesting the role of DNA2 in DSB end resection. Next, we found that depletion of DNA2 impaired phosphorylation of RPA34 as measured by phospho-RPA34 antibody and by a slower migration of RPA34, but it did not affect γ-H2AX formation induced by camptothecin (Fig. 2D). In
the presence of DSBs, both H2AX and RPA34 phosphorylation are regulated by kinases ATM, ATR, and DNA-PK (24, 34, 35). Because RPA is a ssDNA-binding protein and we did not observe impairment of H2AX phosphorylation, we reasoned that reduced RPA34 phosphorylation might be due to inefficient generation of ssDNA and consequently impaired recruitment of RPA34 to DSBs, where it is highly accessible to the kinases, rather than to impaired function of its upstream kinases. Indeed, chromatin fractionation assay showed that in DNA2-deficient cells, binding of both phosphorylated RPA34 and total RPA34 to chromatin was significantly reduced (Fig. 2E). We also found that DNA2 depletion resulted in reduced foci formation of both phosphorylated RPA34 and total RPA34 (Fig. 3A, B, and D), indicating impaired RPA34 recruitment to DNA damage sites. Consistent with this result, we observed significantly reduced activation of CHK1 (Supplementary Fig. S2A) and reduced foci formation of RAD51 (Fig. 3C and D), which are recruited to DSBs after RPA. These data suggested

![Figure 3. DNA2 depletion impairs the recruitment of RPA and RAD51 to replication-associated DSBs.](image-url)
that DNA2 facilitates the recruitment of HR repair factors to DSBs.

Next, we used an I-SceI–inducible recombination assay to assess whether DNA2 depletion affects HR repair (ref. 36; Supplementary Fig. S2B). We found that DNA2 knockdown significantly reduced HR repair efficiency (Fig. 4A). DNA2 contains both a nuclease/ATPase domain and a helicase domain (37). We carried out rescue experiments with RNA interference–resistant wild-type, nuclease-dead (D363A) or helicase-dead DNA2 (K740E) mutants (37). As the mitochondrial localization signal was mapped to amino acids from 734 to 829 (22), we made a DNA2 construct with a specific deletion of this region (DNA2 del734–829), which also disrupts the helicase domain. The abrogation of mitochondrial localization of this construct was confirmed by a mitochondria marker, mtHSP70 (Supplementary Fig. S2C). In the rescue experiments, we found that nuclease activity of DNA2 is required for its function in HR repair, which is independent of its mitochondrial localization (Fig. 4A). The effect of DNA2 on HR repair was not due to the changes in cell-cycle distribution (Supplementary Fig. S2D). We then tested whether the DNA2 mutants would cause dominant-negative effects when they were overexpressed. As we expected, only the nuclease-dead DNA2 mutant impaired cell survival and HR repair (Supplementary Fig. S3A and S3B).

### DNA2 is required for restart of replication forks

Given that DNA2 has enhanced association with replication forks and can promote repair of DSBs by HR, we proposed that DNA2 might enhance cellular tolerance of replication-associated DSBs and promote the restart of stalled or collapsed replication forks. To test this hypothesis, we carried out 3 sets of experiments. First, we analyzed the BrdUrd incorporation by flow cytometry after the release from aphidicolin treatment. We found that DNA2 deficiency impaired normal replication and had a significant impact on the restart of DNA replication after aphidicolin treatment (Fig. 4B). Second, we used immunofluorescent staining to detect BrdUrd incorporation. We observed that DNA2 was required for promoting DNA replication and restart of DNA replication after the removal of replication stress–induced factor aphidicolin (Fig. 4C). Third, we tested the efficiency of restart of replication forks in the absence of DNA2. We first labeled cells with ClDU and then labeled cells with IdU after treatment with aphidicolin. ClDU incorporation indicates unperturbed DNA synthesis (38). In contrast, IdU incorporation correlates with DNA synthesis after the release from DNA replication inhibition. Compared with control cells, DNA2-depleted cells had a reduced proportion of cells with double staining, suggesting impaired restart of replication forks after treatment with replication stress–inducing stimuli (Fig. 4D; Supplementary Fig. S4A).

### DNA2 enhances cellular tolerance of replication-associated DSBs in the context of oncogene activation

Excessive growth signaling induced by oncogene activation is one of the major sources of replication-associated DSBs in cancer cells (2, 4, 5). To elucidate the pathophysiologic relevance of the function of DNA2, we asked whether DNA2 could increase cellular tolerance of replication-associated DSBs induced by oncogene activation. We ectopically expressed H-RAS (V12) and DNA2 in cells and observed that H-RAS expression induced γ-H2AX and p21 formation, which was reduced in the presence of DNA2 (Fig. 5A). Next, we found that H-RAS activation led to a more than 40% reduction in the number of BrdUrd–positive cells (Fig. 5B). This impaired DNA replication was rescued by coexpression of DNA2 (Fig. 5B). We then examined BrdUrd incorporation and γ-H2AX formation to test whether DNA2 might reduce accumulation of replication-associated DSBs induced by oncogene activation. The impaired DNA replication in H-RAS–expressing cells was accompanied by increased γ-H2AX foci formation in BrdUrd–positive cells, which indicated the presence of replication-associated DSBs (Fig. 5C). Interestingly, when DNA2 was coexpressed with H-RAS, cells showed significantly reduced γ-H2AX foci formation in BrdUrd–positive cells, suggesting reduced levels of replication-associated DSBs. These cells consequently had increased BrdUrd incorporation, similar to that in the control cells (Fig. 5C).

On the basis of these observations, we tested whether coexpression of DNA2 would potentiate oncogenic effects of H-RAS activation. By using soft agar assay, we observed that coexpression of H-RAS and DNA2 significantly increased the number of colonies (Fig. 5D). Next, we found that H-RAS expression reduced cell proliferation and cells with DNA2 and H-RAS coexpression had increased cell proliferation (Fig. 5E). This result was further confirmed by using a second cell line expressing a different oncogene, cyclin E (Supplementary Fig. S3C). To summarize, our data revealed that an increase in...
DNA2 expression level may promote HR repair and reduce accumulation of replication-associated DSBs induced by oncogene activation.

**Clinical relevance of DNA2 in cancer**

Given the function of DNA2 in alleviating replication stress induced by oncogene activation, we sought to address the clinical relevance of DNA2 in human cancers. First, by both Oncomine database search (39) and Western blot analysis, we found that cancer cells exhibited increased DNA2 mRNA expression (Fig. 6A) and protein expression (Fig. 6B). DNA2 expression was also upregulated in MCF10AT cells, which represent atypical hyperplasia, a premalignant disease observed early in the natural course of breast cancer development (Fig. 6C). We further examined DNA2 expression in a cell model representing a series of transitions from normal pancreatic ductal cells to cancer cells due to activating K-RAS (16). Again, we found that overexpression of DNA2 occurred at an early stage of transformation (Fig. 6C). More importantly, we found that DNA2 mRNA levels were significantly increased in a wide range of cancer types reported from independent research groups in the Oncomine database (ref. 39; Fig. 6D).

Pancreatic ductal adenocarcinoma has been found to almost always contain K-RAS mutations (>95% of tumors; 40). We specifically tested DNA2 expression in human tissues from pancreatic ductal adenocarcinoma. As we anticipated, DNA2 expression was increased in cancer tissues compared with adjacent normal tissues (Fig. 7A). We also found that DNA2 expression was positively correlated with the histologic grade of ovarian cancer (Fig. 7B). This finding suggested that elevated DNA2 expression might be functionally associated with increased intrinsic genomic instability during cancer development. To further test this possibility, we examined whether DNA2 expression exhibited a distinct pattern in different subtypes of breast cancer. On the basis of gene expression profiling, breast cancer can be divided into 5 subtypes: basal-like, Her2-positive, luminal A, luminal B, and normal breast-like (41). Morphologically, basal-like breast cancers have higher histologic grade than the other subtypes, and molecularly,
basal-like breast cancers exhibit a higher degree of genomic instability, which is manifested by increased numbers of mutations, translocations, and single-nucleotide polymorphisms (42). As we expected, DNA2 expression in breast cancer cohort (Netherlands Cancer Institute: NKI cohort, n = 295) was significantly higher in basal-like breast cancer than in the other subtypes (Fig. 7C). Indeed, in patients with breast cancer, DNA2 expression was positively correlated with the likelihood of breast cancer metastasis and was inversely correlated with the duration of overall patient survival (Fig. 7C).
To further determine the biologic effects of enhanced expression of DNA2 in cancer cells, we depleted DNA2 in breast cancer MCF7 cells. DNA2 knockdown significantly increased DSB formation and reduced cell proliferation (Supplementary Fig. S4B). Interestingly, in another cancer cell line U2OS cells, which have competent DDR, DNA2-deficient cells were remarkably larger than control cells (Supplementary Fig. S4C) and exhibited a flat morphologic change. This observation led us to test whether DNA2 deficiency activates the senescence pathway, which permanently withdraws cells from the cell cycle. Compared with control cells, DNA2-depleted cells showed activation of γ-H2AX, phosphorylation and stabilization of p53, and activation of p21 (Supplementary Fig. S4D). DNA2 knockdown induced senescence as shown by β-galactosidase staining (Supplementary Fig. S4E). Notably, the number of senescent cells was remarkably reduced in the presence of aphidicolin (Supplementary Fig. S4E). Because DNA2 has been reported to regulate mitochondrial DNA replication and repair (22), we excluded the possibility that DNA2 depletion could cause mitochondria dysfunction and produce higher levels of reactive oxygen species (ROS), which could also contribute to cellular senescence (Supplementary Fig. S5).

**Discussion**

In summary, we propose a model in which DNA2 is associated with factors involved in DNA replication and accumulation at stalled or collapsed replication forks. One likely function of DNA2 nuclease is in ssDNA formation at stalled replication forks, which allows RPA and RAD51 loading and subsequent HR repair to restart the stalled replication forks. Thereby, DNA2 can alleviate replication stress, primarily by facilitating HR repair of replication-associated DSBs (Fig. 7D). Our finding that DNA2 interacts with polymerase δ, which is thought to be the main polymerase involved in lagging strand synthesis, is consistent with previous observations of DNA2 function in processing Okazaki fragment in yeast (43, 44). It is notable that compared with leading strand synthesis, lagging strand synthesis is associated with a greater risk of aberrant replication and genome instability because a large number of Okazaki fragments need to be processed and ligated (20). It is very likely that DNA2, besides resection, has a role in preventing excessive DNA damage by processing 5′ flaps formed during lagging strand synthesis or during HR. It is believed that DSBs are initially sensed by ATM, which is followed by end resection generating ssDNA for RPA loading and activation of ATR (35). As Xenopus DNA2 is found to be in a complex with ATM (21), whether the nuclease activity of DNA2 and the accumulation of DNA2 at DSB ends require ATM signaling requires further investigation.

Our data link the evolutionarily conserved function of DNA2 in HR repair to its role in alleviating both chemical- and oncogene-induced replication stress (2–5). During
tumorigenesis, excessive growth signals often lead to hyper-proliferation of cancer cells, which results in replication stress and increased formation of replication-associated DSBs. In our study, we have identified that enhanced DSB resection activity such as mediated by increased DNA2 expression may facilitate HR repair, which constitutes a key step to enhance cellular tolerance of replication-associated DSBs and provides cancer cells with a survival advantage. Currently, by using a mouse genetic interaction approach, we are establishing a DNA2 conditional knockout mouse model to test this hypothesis in vivo.

We speculate that our findings may have significant clinical implications for cancer management. First, DSBs associated with oncogene-induced replication stress are observed in large fractions of early lesions from various human cancer tissues. Activation of the DSB end resection pathway such as DNA2 overexpression might serve as a marker for genetic alterations in premalignant lesions that promote tumor progression. Second, our findings raise the intriguing possibility that nucleases/helicases involved in DSB end resection, which are highly expressed in a wide range of human cancers, could serve as a new class of therapeutic targets. Indeed DNA nucleases/ helicases are intensively studied as potential anti-cancer targets. Lately, a small-molecule inhibitor of the WRN helicase was identified, therefore similar strategy should be possible for DNA2 enzyme (45–48). Third, recent studies showed excellent response of BRCA1/BRCA2-mutated tumors with HR repair deficiency to PARP inhibitors (49, 50). Currently, multiple clinical trials are testing the efficacy of PARP inhibitors in treating triple-negative breast cancer, which clinically and molecularly resembles BRCA1/BRCA2-mutated tumors (51, 52). Our data showed that basal-like breast cancer, which largely overlaps with triple-negative breast cancer, had significantly higher expression levels of DSB end resection factor DNA2. These factors and the activity of DSB end resection might provide a candidate biomarker to predict the response of triple-negative breast cancer to PARP inhibitors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: G. Peng, R. Y.-I. Tsai, G. Ira, S.-Y. Lin
Development of methodology: G. Peng
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Peng, H. Dai, H.-J. Hsieh, I. Bedrosian
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Peng, Y.-Y. Park, J.-S. Lee
Writing, review, and/or revision of the manuscript: G. Peng, G. Ira, S.-Y. Lin
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Peng, W. Zhang, M.-R. Pan
Study supervision: G. Peng, S.-Y. Lin

Acknowledgments

The authors thank S. Deming for proofreading the manuscript; M. Jasin for reagents; and M. D. Anderson Cancer Center core facilities for mass spectrometry, FACS, and molecular cytogenetics.

Grant Support

This work was, in part, supported by NCI grant R01 CA112291 and DoD Era of Hope Scholar Award (WRXWH1-10-1-0558) to S.-Y. Lin, NIIH grant GM080600 to G. Ira, postdoctoral fellowship from Susan Komen Foundation for the Cure to G. Peng, and NCI grant K99 CA119186 to G. Peng.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertising in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 23, 2011; revised February 28, 2012; accepted March 19, 2012; published OnlineFirst April 9, 2012.

References


www.aacrjournals.org Cancer Res; 2012 OF11
Peng et al.

Human Nuclease/Helicase DNA2 Alleviates Replication Stress by Promoting DNA End Resection

Guang Peng, Hui Dai, Wei Zhang, et al.

Cancer Res  Published OnlineFirst April 9, 2012.

Updated version  Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-11-3152

Supplementary Material  Access the most recent supplemental material at:
http://cancerres.aacrjournals.org/content/suppl/2012/04/09/0008-5472.CAN-11-3152.DC1

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.