PROSPECT
Journal of Cellular Biochemistry 106:758–763 (2009)

Journal of Cellular Biochemistry

Hitting the Bull's Eye: Novel Directed Cancer Therapy Through Helicase-Targeted Synthetic Lethality

Monika Aggarwal and Robert M. Brosh Jr.*

Laboratory of Molecular Gerontology, National Institute on Aging, NIH, NIH Biomedical Research Center, 251 Bayview Drive, Baltimore, Maryland 21224

ABSTRACT

Designing strategies for anti-cancer therapy have posed a significant challenge. One approach has been to inhibit specific DNA repair proteins and their respective pathways to enhance chemotherapy and radiation therapy used to treat cancer patients. Synthetic lethality represents an approach that exploits pre-existing DNA repair deficiencies in certain tumors to develop inhibitors of DNA repair pathways that compensate for the tumor-associated repair deficiency. Since helicases play critical roles in the DNA damage response and DNA repair, particularly in actively dividing and replicating cells, it is proposed that the identification and characterization of synthetic lethal relationships of DNA helicases will be of value in developing improved anti-cancer treatment strategies. In this review, we discuss this hypothesis and current evidence for synthetic lethal interactions of eukaryotic DNA helicases in model systems. J. Cell. Biochem. 106: 758–763, 2009. Published 2009 Wiley-Liss, Inc.†

KEY WORDS: SYNTHETIC LETHALITY; HELICASE; CANCER THERAPY; DNA REPAIR; ANTI-CANCER DRUG

Cells exposed to DNA damage have multiple pathways in order to cope with the stressed condition. DNA repair is believed to represent a good target for enhancing cancer treatment strategies that are based on chemotherapy drugs or radiation that induce death of rapidly proliferating cells. There is a growing interest in synthetic lethality of compensating DNA repair pathways as a strategy to target cancer therapies based on the genetic background of the tumor. Since helicases play an integral role in the DNA damage response, it seems reasonable that this particular class of proteins may be one of the optimal bull's eye targets for cancer therapy based on synthetic lethality (Fig. 1). Specifically, compensatory repair pathways mediated by DNA helicases are a priority for further studies. Research in the basic sciences has demonstrated and characterized synthetic lethal interactions of eukaryotic DNA helicases. This work is likely to serve as a foundation for the development of anti-cancer therapies that utilize small molecule helicase inhibitors or antagonists to helicase gene expression such as RNA interference.

HITTING THE BULL'S EYE—A CHALLENGE FOR CANCER THERAPY

There has been considerable discussion during the last several years that DNA repair proteins and pathways might be suitable targets for anti-cancer strategies (see review series published in May 2008 in *Anti-Cancer Agents-Medicinal Chemistry*) [Adhikari et al., 2008; Bernstein et al., 2008; Brosh, 2008; Casorelli et al., 2008; Dexheimer et al., 2008; Gupta and Brosh, 2008; Kelley and Fishel, 2008; Litman et al., 2008; Maga and Hubscher, 2008; Powell and Kachnic, 2008; Sakamoto-Hojo and Balajee, 2008]. The principal concept is that the traditional therapies to battle cancer are largely based on treatments of patients with DNA damaging agents or radiation to kill the rapidly proliferating tumorigenic cells. However, a number of complicating factors contribute to the reduced effectiveness of cancer therapies based on DNA damage-induced cell killing. Hitting the bull's eye to achieve the goal of total elimination of the cancer without serious side-effect remains a huge challenge to both scientists and clinicians.

What factors and issues compromise the accuracy of the archer seeking to deliver with precision a direct strike at the bull's eye? There are a number of potential caveats of conventional anti-cancer therapies relying on the administration of DNA damaging chemotherapy drugs or direct radiation of tumors [Allan and Travis, 2005; Helleday et al., 2008]. The cytotoxic effects of such treatments on normal cells pose a significant threat to cancer patients. Tumors can become resistant to radiotherapy or chemotherapy. Cancer cells have the mysterious ability to maintain their active proliferation by up-regulating DNA damage response

Grant sponsor: Intramural Research Program of the NIH; Grant sponsor: National Institute on Aging.

*Correspondence to: Robert M. Brosh, Jr., Laboratory of Molecular, Gerontology, NIA, NIH, NIH Biomedical Research Center, 251 Bayview Drive, Suite 100, Rm #06B125, Baltimore, MD 21224. E-mail: broshr@mail.nih.gov
Received 9 December 2008; Accepted 10 December 2008 • DOI 10.1002/jcb.22048 • 2009 Wiley-Liss, Inc.
Published online 27 January 2009 in Wiley InterScience (www.interscience.wiley.com).

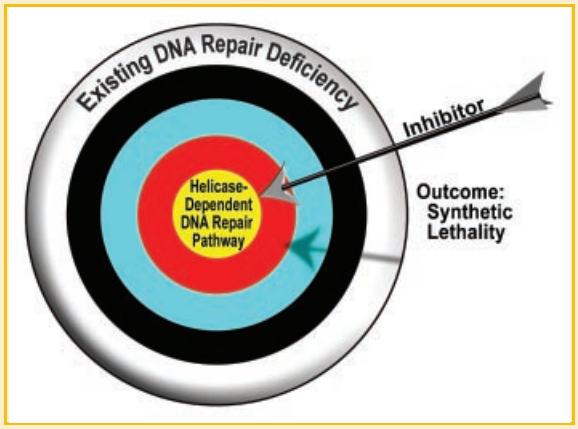

Fig. 1. Bull's eye for cancer therapy: helicase-targeted synthetic lethality. Compensatory helicase-dependent DNA repair pathways may represent a suitable target for anti-cancer therapy strategies that are designed to introduce DNA damage to tumors with pre-existing defined DNA repair deficiencies. See text for details.

and DNA repair pathways that enable the cells to circumvent their ultimate demise that would normally occur as a consequence of the accumulation of replicative DNA lesions that are themselves lethal or induce apoptotic cell death. Moreover, the concentration of drug or dose of radiation can be toxic to normal non-cancerous cells due to impairment of DNA replication or transcription, leading to a rapid decline in tissue and organ function. This situation has challenged cancer biologists to determine a therapeutic index of DNA repair inhibitors for a given drug or radiation treatment to improve the efficacy of the anti-cancer treatment strategy.

Thus, DNA repair proteins and pathways might be suitable targets for inhibition to enhance the current chemotherapeutic options. However, certain issues still exist such as the cytotoxic effects of DNA repair inhibitors on normal cells as well as the elevated genomic instability resulting from interference of DNA repair pathways. Since mammalian cells rely heavily on DNA repair to protect against DNA damaging agents used for chemotherapy, therapy-related carcinogenesis leading to secondary primary cancers is a significant risk. In order for DNA repair inhibition to enhance anti-cancer therapy, the targets will have to be carefully chosen and hit with precision, leading us back to the bull's eye analogy.

SYNTHETIC LETHALITY: A PROMISING APPROACH FOR TAILORED STRATEGIES TO FIGHT CANCER

To maximize the synergistic effects of DNA damaging agents and DNA repair inhibitors, it would be helpful to determine the genetic background of the tumor. Because of the mutagenic nature of cancer, tumors typically already have deficiencies in certain DNA repair pathways. However, compensatory pathways of DNA repair may prevail, and reduce the effectiveness of the drug treatment. The concept of synthetic lethality whereby inhibition of a DNA repair pathway in a tumor already deficient for a given repair pathway may prove to be an effective strategy for novel cancer therapies. In fact, a proof-of-principal for this approach has been realized with the discovery by Helleday, Ashworth, and colleagues that inhibitors of the single-stranded break (SSB) DNA repair protein poly (ADP)-ribose polymerase (PARP)1 are synthetic lethal in HR deficient cells with mutations in breast cancer susceptibility proteins BRCA1 or BRCA2 [Bryant et al., 2005; Farmer et al., 2005]. In this case, it is believed that when PARP1 is inhibited, SSBs persist which lead to the collapse of replication forks in dividing cells that ultimately result in potentially toxic double-strand breaks (DSB). In BRCA-deficient cells, the absence of homologous recombination (HR) which normally provides an error-free pathway to deal with replication fork associated lesions results in cell killing by concentrations of PARP inhibitor that are not toxic to HR-proficient cells. This elegant discovery has paved the way for researchers to study synthetic lethality as an improved mechanism for cancer therapy. In fact, clinical trials using PARP inhibitors are currently in progress [Lord and Ashworth, 2008]. Deficiency in other HR repair proteins also sensitizes cells to PARP inhibitors [McCabe et al., 2006], suggesting that by targeting compensatory DNA repair pathways, DNA damaging therapy or ionizing radiation may be tailored to the specific genetic makeup of the individual and/or tumor.

CAN SYNTHETIC LETHALITY BE ACHIEVED THROUGH THE INHIBITION OF HELICASE-DEPENDENT DNA REPAIR PATHWAYS?

Now, numerous DNA repair proteins have been investigated for their utility as targets to enhance cancer therapy options. The classes of potential DNA repair targets include those that are involved in base excision repair (BER), the BRCA-Fanconi Anemia (FA) pathway, DNA damage signaling kinases, mismatch repair proteins, nucleotide excision repair, and DSB repair (HR and nonhomologous end-joining (NHEJ)) [Helleday et al., 2008]. Given the prominence of the HR pathway of DSB repair to deal with replication associated lesions that accumulate in rapidly proliferating cells, we hypothesize that DNA helicases which are known to have fundamentally important roles in HR represent a strong class of potentially suitable DNA repair targets [Gupta and Brosh, 2007, 2008]. Keeping in mind the power of synthetic lethality, we will discuss some pertinent reports in the literature that identify and characterize helicase-dependent pathways and genetic interactions that might lead to novel approaches for cancer therapy. We will begin this discussion with instrumental studies in yeast that have identified key DNA repair helicases followed by a description of some useful higher eukaryotic systems providing insight to helicase determinants of synthetic lethality. This work will be placed in the context of potentially enhancing cancer therapeutic options.

SYNTHETIC LETHALITY: USING YEAST TO EXPLORE HELICASE NETWORKS

A landmark article that began the era for investigation of DNA helicase genetic networks was published in 2003 from the Boeke lab

[Ooi et al., 2003]. In this article, the Sgs1 and Srs2 3′–5′ DNA helicases of *Saccharomyces cerevisiae* were investigated for their genetic interactions by a technique known as synthetic lethal analysis by microarray (SLAM). This approach enabled the investigator to identify genome-wide interactions with the helicase (or any other gene) in question using a facile methodology, and also ranked candidate genetic interactions. The results from the study by the Boeke lab suggested different roles for Srs2 and Sgs1 in the response to replicational stress. Srs2 was predicted to operate in a damaged DNA replication fork processing role, whereas Sgs1 was more specifically tailored to have roles in rDNA replication, DNA topology, or lagging strand synthesis. Moreover, Sgs1 and Srs2 were predicted to operate in parallel pathways in a DNA damage checkpoint pathway by separately transducing the replicational stress signal. Overall, this study provided a first proof of principle that helicase genetic interaction networks exist and can be dissected. Moreover, the results were consistent with earlier evidence that the synthetic lethal interaction of *srs2* and *sgs1* [Lee et al., 1999] can be attributed to accumulation of toxic recombination intermediates that can be suppressed by the additional loss of HR genes *RAD51* or *RAD54* [Gangloff et al., 2000].

In 2005, the Campbell lab employed a synthetic genetic array analysis (SGA) using *DNA2* as the query yeast helicase gene [Budd et al., 2005]. Dna2 is best-known for its role during Okazaki fragment processing, a key aspect of cellular lagging strand DNA replication. Using two well-known conditional alleles of *DNA2*, 43 synthetic lethal or synthetic sick genetic interactions were identified and validated. Further analysis of the *DNA2* gene-interacting pathways defined a network of proteins previously implicated to operate at the replication fork and important for genomic stability. These included proteins involved in the processes of Okazaki fragment processing, DNA repair, and chromatin remodeling. *DNA2* genetically interacted with polymerase delta, other DNA helicases, and genes that are synthetic lethal with *srs2* and *sgs1*. Like the Boeke study [Ooi et al., 2003], the Campbell study identified the 5′–3′ helicase Rrm3 as a critical hub in the helicase network, suggesting that Rrm3 prevents the accumulation of toxic recombination or replication intermediates. Importantly, the work suggested that Dna2 and other helicases (Sgs1, Srs2, Rrm3) form a complex interacting network with other DNA replication, repair, and recombination proteins to preserve genomic integrity at the replication fork.

The ongoing work in yeast to investigate synthetic lethal interactions among genes involved in cellular nucleic acid metabolism will likely provide new platforms to explore functionally conserved proteins and pathways in higher eukaryotes. The value of yeast as a model organism to study helicase gene networks cannot be underestimated, given the growing evidence that conserved response pathways to DNA damage and replicational stress exist between yeast and mammalian cells. Targeted cancer therapies which exploit synthetic lethal relationships between proteins acting in DNA repair pathways of rapidly proliferating cells can be modeled and devised based on the findings from yeast screens. Of particular interest are the helicase networks since evidence implicates these pathway webs as critically essential for stability at the replication fork and an appropriate DNA damage and signaling response. Pinpointed disruption of helicase-dependent pathways may provide the fine-tuning necessary to use synthetic lethality as a mechanism for killing cancer cells in a selective manner.

HELICASE DETERMINANTS OF SYNTHETIC LETHALITY IN EUKARYOTIC MODEL SYSTEMS

Although the complexity of gene networks may increase from unicellular to multicellular organisms, basic pathways of DNA replication and repair are often conserved. In this section, we highlight several advances in identifying and understanding synthetic lethal relationships of various eukaryotic DNA helicases and interacting proteins that are engaged in processes that directly affect replication fork dynamics and genomic stability. We will discuss a representative example from a few model organisms, beginning with another simple eukaryote and proceeding with more complex higher eukaryotic systems.

NEUROSPORA RECQ HOMOLOGS QDE3, AND RECQ2

Two RecQ homologs exist in the filamentous fungus *Neurospora*, QDE3, and RECQ2 [Cogoni and Macino, 1999; Pickford et al., 2003]. Kato and Inoue [2006] determined that the *qde-3 recQ2* double mutant showed a severe growth defect and increased sensitivity to a variety of DNA damaging agents compared to the single mutants, suggesting the two RecQ helicases operate in parallel pathways of the DNA damage response. Importantly, the growth defect of the *qde-3 recQ2* double mutant was suppressed by a third mutation in the *RAD51* homolog *mei-3*. The increased mutator phenotype of the *qde-3 recQ2* double mutant was suppressed by mutation in the mammalian Ku80 homolog *mus52*, suggesting that error-prone NHEJ is responsible for the elevated mutation frequency of the *qde-3 recQ2* double mutant. However, the growth defect of the *qde-3 recQ2* double mutant was not suppressed by the *mus52* mutation, consistent with the idea that HR is responsible. Based on their genetic results, the authors proposed that the two RecQ homologs in *Neurospora* play a role in the suppression of spontaneous DSBs. Given the strong interest in DNA strand break repair as a target for inhibition in anti-cancer strategies, the genetic interactions between RecQ genes demonstrated in *Neurospora* and other model systems are likely to be relevant.

DROSOPHILA BLM

A common theme in helicase functions during cellular replication or repair is the interaction of these proteins with structure-specific nucleases. A good example of the myriad of physical and functional interactions between helicases and nucleases is that of the RecQ helicases and Rad2 nucleases [Sharma et al., 2008]. WRN helicase, defective in Werner syndrome, stimulates the DNA cleavage activity catalyzed by Flap Endonuclease 1 (FEN1), a nuclease that is implicated in Okazaki fragment processing and BER, through a physical protein interaction [Brosh et al., 2001, 2002]. The WRN: FEN1 interaction was shown to be important in cellular DNA replication in vivo [Sharma et al., 2004b], and the two proteins are closely associated with each other in human cells at arrested

replication forks [Sharma et al., 2004a]. BLM was also show to interact with FEN1 [Sharma et al., 2003b]. Protein interactions of the FEN1 sequence-related EXO1 nuclease with WRN [Sharma et al., 2003a], RECQ1 [Doherty et al., 2005], and BLM [Nimonkar et al., 2008] also exist that are likely to be important for strand resection during DSB repair or processing of stalled replication fork structures to prevent deleterious recombinogenic pathways. Understanding how these interactions are regulated in a biological setting is a daunting but important challenge. It is quite likely that synthetic lethal interactions exist between helicases and nucleases that might be exploited for cancer therapies.

In *Drosophila*, mutation in the gene encoding the Mus81 endonuclease is synthetic lethal with mutation in the *mus309* gene encoding the BLM helicase, and the synthetic lethality is associated with elevated apoptosis in rapidly proliferating tissues [Trowbridge et al., 2007]. Elevated apoptosis from the increased load of DNA damage leads to cell death, particularly in rapidly dividing cells. The authors of the study proposed that the broken replication forks in the *mus81 mus309* double mutant arise from replication blockage that leads to the accumulation of double strand breaks. These DSBs are likely to undergo deleterious pathways of recombination, leading to further genomic instability. Consistent with this notion, the synthetic lethality of the *mus81 mus309* double mutant was suppressed by a third mutation in the DNA strand exchange protein Rad51 that is implicated in HR. Altogether, the results from the genetic assays in *Drosophila* are consistent with the previously observed synthetic lethal interactions of RecQ helicases (*SGS1*, *rqh1*) and genes encoding the Mus81-Mms4 (or Mus81-Eme1) nuclease complexes in *S. cerevisiae* and *Schizosaccharomyces pombe* [Boddy et al., 2000; Mullen et al., 2001]. Interestingly, human Mus81 nuclease interacts physically and functionally with the BLM helicase [Zhang et al., 2005], suggesting the helicase operates in a complex network of proteins that work through overlapping and interacting pathways to confer genomic integrity.

CAENORHABDITIS ELEGANS RTEL1

The groundwork evidence implicating Srs2 as a key helicase in the DNA damage response in *S. cerevisiae* suggests that it might be an excellent target for studying synthetic lethal interactions of *srs2* in mammalian cells. However, the functional homolog of Srs2 in higher eukaryotes was not known until only very recently. Barber et al. [2008] identified *C. elegans* RTEL-1 as a functional analog of Srs2; furthermore, they characterized human RTEL1, and determined that it is necessary for DNA repair and to suppress HR. In terms of synthetic lethality, *C. elegans rtel-1* mutants displayed high embryonic lethality when present with a second mutation in helicase genes *him-6* (BLM) or *rcq-5* (RECQ5), or the *mus81* gene encoding the structure-specific nuclease mentioned earlier [Barber et al., 2008]. *rtel-1* mutants lacking *dog-1* (FANCJ) helicase produced no embryos, indicating their strong genetic interaction [Barber et al., 2008]. Based on the synthetic lethal interactions, the authors suggested that RTEL-1, like Srs2, functions to regulate HR. In support of this concept, RAD51 foci in the worm germ-line were massively elevated in *rtel-1* mutants that also contained mutations in genes representing synthetic lethal interactions (*him-6*, *rcq-5*, *mus81*, *dog-1*). Importantly, RTEL1-depleted human cells showed increased HR and sensitivity to interstrand cross-linking (ICL)-inducing agent, similar to what was observed for the *C. elegans rtel-1* mutant. Human RTEL1 was shown to biochemically inhibit HR by disrupting the three-stranded D-loop DNA molecule [Barber et al., 2008], an early intermediate of HR. Altogether, the results suggest that RTEL1 controls HR to prevent genomic instability and raise the possibility that RTEL1 is a good candidate for targeted cancer therapies based on synthetic lethality.

VERTEBRATE BLM, RECQL5, AND F-BOX DNA HELICASE 1

Studies in *S. pombe* demonstrating synthetic lethality between the sole RecQ homolog Rqh1 and F-box DNA helicase 1 (Fbh1) [Morishita et al., 2005; Osman et al., 2005] prompted Takeda and co-workers to examine the potential relationship between FBH1 and BLM in chicken cells [Kohzaki et al., 2007]. The chicken DT40 system has provided an elegant and facile system to study the pathways of various proteins implicated in cellular DNA metabolism in vertebrates. In addition to chicken, FBH1 is conserved in mice and humans as well. $FBH1^{-/-}$ cells were observed to exhibit elevated sister chromatid exchange (SCE) and formation of radial chromosomes [Kohzaki et al., 2007]. $BLM^{-/-}/FBH1^{-/-}$ cells displayed additive increases in SCEs and formation of radial chromosomes, suggesting that BLM and Fbh1 helicases operate in parallel pathways to avoid crossovers during recombination initiated by replication fork collapse.

Gene disruption studies in vertebrate cells have shed new insight to the overlapping functions and pathways of eukaryotic RecQ helicases. SCE is increased in an additive manner when both BLM and RECQL5 are mutated in either chicken DT40 cells or mouse cells [Wang et al., 2000; Hu et al., 2005; Otsuki et al., 2007], indicating that the two RecQ helicases suppress SCE by distinct mechanisms. Moreover, $BLM^{-/-}/RECL5^{-/-}$ and $BLM^{-/-}/FBH1^{-/-}$ DT40 cells grow more slowly than cells with a single gene disruption [Kohzaki et al., 2007]. Although DT40 cells deleted for both *BLM* and *RECQL1* did not show a higher SCE level compared to the $BLM^{-/-}$ single mutant, $BLM^{-/-}/RECL1^{-/-}$ cells displayed a hyper-SCE phenotype when cells were treated with the ICL agent mitomycin C [Wang et al., 2003]. Thus, like the lower eukaryotes, BLM helicase seems to operate as a network hub or molecular node in terms of overlapping and intersecting genetic pathways to confer stability of the replicating genome (Fig. 2). For example, BLM and its associated factors (RPA, Topoisomerase IIIα) are found in a supercomplex with the Fanconi anemia core complex [Wang, 2007]. Previous findings have suggested that BLM collaborates with FA proteins in response to replicational stress [Pichierri et al., 2004; Hirano et al., 2005]. The development of inhibitors against BLM and related helicases is likely to be a useful approach in exploiting synthetic lethality and compensatory DNA repair pathways to create novel cancer therapy strategies. Targeted helicase inhibition may enable the use of conventional anti-cancer drugs like DNA ICL agents at lower concentrations, thereby broadening the therapeutic index. Moreover, DNA helicases may well be an attractive target for amplification of tumor-specific replicative lesions through targeted inhibition of DNA repair proteins, a hotly discussed area of cancer therapy [Helleday, 2008].

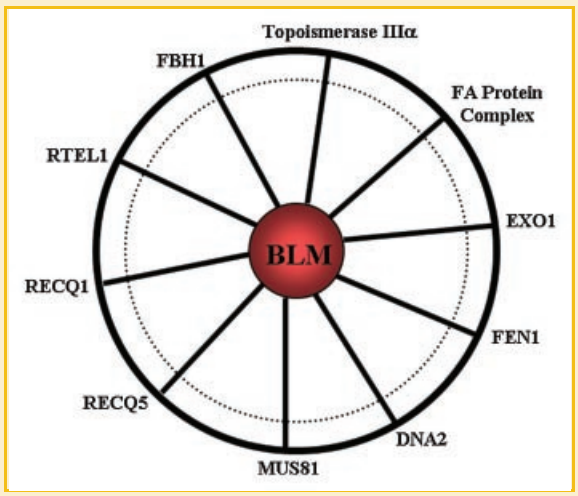

Fig. 2. Bloom's syndrome helicase (BLM) operates as a network hub. Physical, functional, and genetic interactions of the BLM helicase suggest that BLM is a network hub for overlapping and intersecting pathways to maintain genomic stability and conduct the replicational stress response. Therefore, BLM and its interacting network represent a provocative target for anti-cancer drugs to inhibit compensatory DNA repair pathways. See text for details.

CONCLUSIONS AND FUTURE DIRECTIONS

Future research in helicase-targeted therapy will be benefited by mouse model systems that will hopefully more closely mimic tumor progression and inhibition in humans. However, given the limitations of mice in terms of their differences from humans in certain aspects of genomic DNA structure and metabolism (e.g., longer telomeres), continued work with human cells and xenografts will be extremely important for cancer biologists. RNA interference screens, such as that described by Lord et al. [2008] [Lord and Ashworth, 2008], to identify DNA repair determinants of PARP inhibitor sensitivity will be a valuable approach to investigate the potential importance of helicase targets to enhance anti-cancer drug sensitivity. In addition, research efforts should be maintained and supported in model eukaryotic genetic systems since these have provided important insights to the identification and characterization of synthetic lethal relationships between DNA repair pathways. No doubt, hitting the bull's eye to develop novel therapies for cancer will require significant effort, but DNA repair helicases offer an enticing target for cancer drugs of the future.

REFERENCES

Adhikari S, Choudhury S, Mitra PS, Dubash JJ, Sajankila SP, Roy R. 2008. Targeting base excision repair for chemosensitization. Anticancer Agents Med Chem 8:351–357.

Allan JM, Travis LB. 2005. Mechanisms of therapy-related carcinogenesis. Nat Rev Cancer 5:943–955.

Barber LJ, Youds JL, Ward JD, McIlwraith MJ, O'Neil NJ, Petalcorin MI, Martin JS, Collis SJ, Cantor SB, Auclair M, Tissenbaum H, West SC, Rose AM, Boulton SJ. 2008. RTEL1 maintains genomic stability by suppressing homologous recombination. Cell 135:261–271.

Bernstein NK, Karimi-Busheri F, Rasouli-Nia A, Mani R, Dianov G, Glover JN, Weinfeld M. 2008. Polynucleotide kinase as a potential target for enhancing cytotoxicity by ionizing radiation and topoisomerase I inhibitors. Anticancer Agents Med Chem 8:358–367.

Boddy MN, Lopez-Girona A, Shanahan P, Interthal H, Heyer WD, Russell P. 2000. Damage tolerance protein Mus81 associates with the FHA1 domain of checkpoint kinase Cds1. Mol Cell Biol 20:8758–8766.

Brosh RM, Jr. 2008. DNA repair as a target for anti-cancer therapy. Anticancer Agents Med Chem 8:350.

Brosh RM, Jr., von Kobbe C, Sommers JA, Karmakar P, Opresko PL, Piotrowski J, Dianova I, Dianov GL, Bohr VA. 2001. Werner syndrome protein interacts with human Flap Endonuclease 1 and stimulates its cleavage activity. EMBO J 20:5791–5801.

Brosh RM, Jr., Driscoll HC, Dianov GL, Sommers JA. 2002. Biochemical characterization of the WRN-FEN-1 functional interaction. Biochemistry 41:12204–12216.

Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, Helleday T. 2005. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 434:913–917.

Budd ME, Tong AH, Polaczek P, Peng X, Boone C, Campbell JL. 2005. A network of multi-tasking proteins at the DNA replication fork preserves genome stability. PLoS Genet 1:e61.

Casorelli I, Russo MT, Bignami M. 2008. Role of mismatch repair and MGMT in response to anticancer therapies. Anticancer Agents Med Chem 8:368–380.

Cogoni C, Macino G. 1999. Posttranscriptional gene silencing in Neurospora by a RecQ DNA helicase. Science 286:2342–2344.

Dexheimer TS, Antony S, Marchand C, Pommier Y. 2008. Tyrosyl-DNA phosphodiesterase as a target for anticancer therapy. Anticancer Agents Med Chem 8:381–389.

Doherty KM, Sharma S, Uzdilla L, Wilson TM, Cui S, Vindigni A, Brosh RM, Jr. 2005. RECQ1 helicase interacts with human mismatch repair factors that regulate gentic recombination. J Biol Chem 280:28025–28094.

Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. 2005. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917–921.

Gangloff S, Soustelle C, Fabre F. 2000. Homologous recombination is responsible for cell death in the absence of the Sgs1 and Srs2 helicases. Nat Genet 25:192–194.

Gupta R, Brosh RM, Jr. 2007. DNA repair helicases as targets for anti-cancer therapy. Curr Med Chem 14:503–517.

Gupta R, Brosh RM, Jr. 2008. Helicases as prospective targets for anti-cancer therapy. Anticancer Agents Med Chem 8:390–401.

Helleday T. 2008. Amplifying tumour-specific replication lesions by DNA repair inhibitors—A new era in targeted cancer therapy. Eur J Cancer 44:921–927.

Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. 2008. DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 8:193–204.

Hirano S, Yamamoto K, Ishiai M, Yamazoe M, Seki M, Matsushita N, Ohzeki M, Yamashita YM, Arakawa H, Buerstedde JM, Enomoto T, Takeda S, Thompson LH, Takata M. 2005. Functional relationships of FANCC to homologous recombination, translesion synthesis, and BLM. EMBO J 24:418–427.

Hu Y, Lu X, Barnes E, Yan M, Lou H, Luo G. 2005. Recql5 and Blm RecQ DNA helicases have nonredundant roles in suppressing crossovers. Mol Cell Biol 25:3431–3442.

Kato A, Inoue H. 2006. Growth defect and mutator phenotypes of RecQ-deficient Neurospora crassa mutants separately result from homologous recombination and nonhomologous end joining during repair of DNA double-strand breaks. Genetics 172:113–125.

Kelley MR, Fishel ML. 2008. DNA repair proteins as molecular targets for cancer therapeutics. Anticancer Agents Med Chem 8:417–425.

Kohzaki M, Hatanaka A, Sonoda E, Yamazoe M, Kikuchi K, Vu TN, Szuts D, Sale JE, Shinagawa H, Watanabe M, Takeda S. 2007. Cooperative roles of vertebrate Fbh1 and Blm DNA helicases in avoidance of crossovers during recombination initiated by replication fork collapse. Mol Cell Biol 27:2812–2820.

Lee SK, Johnson RE, Yu SL, Prakash L, Prakash S. 1999. Requirement of yeast SGS1 and SRS2 genes for replication and transcription. Science 286:2339–2342.

Litman R, Gupta R, Brosh RM, Jr., Cantor SB. 2008. BRCA-FA pathway as a target for anti-tumor drugs. Anticancer Agents Med Chem 8:426–430.

Lord CJ, Ashworth A. 2008. Targeted therapy for cancer using PARP inhibitors. Curr Opin Pharmacol 8:363–369.

Lord CJ, McDonald S, Swift S, Turner NC, Ashworth A. 2008. A high-throughput RNA interference screen for DNA repair determinants of PARP inhibitor sensitivity. DNA Repair (Amst) 7:2010–2019.

Maga G, Hubscher U. 2008. Repair and translesion DNA polymerases as anticancer drug targets. Anticancer Agents Med Chem 8:431–447.

McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, Giavara S, O'Connor MJ, Tutt AN, Zdzienicka MZ, Smith GC, Ashworth A. 2006. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to Poly(ADP-ribose) polymerase inhibition. Cancer Res 66:8109–8115.

Morishita T, Furukawa F, Sakaguchi C, Toda T, Carr AM, Iwasaki H, Shinagawa H. 2005. Role of the Schizosaccharomyces pombe F-Box DNA helicase in processing recombination intermediates. Mol Cell Biol 25:8074–8083.

Mullen JR, Kaliraman V, Ibrahim SS, Brill SJ. 2001. Requirement for three novel protein complexes in the absence of the Sgs1 DNA helicase in Saccharomyces cerevisiae. Genetics 157:103–118.

Nimonkar AV, Ozsoy AZ, Genschel J, Modrich P, Kowalczykowski SC. 2008. Human exonuclease 1 and BLM helicase interact to resect DNA and initiate DNA repair. Proc Natl Acad Sci USA 105:16906–16911.

Ooi SL, Shoemaker DD, Boeke JD. 2003. DNA helicase gene interaction network defined using synthetic lethality analyzed by microarray. Nat Genet 35:277–286.

Osman F, Dixon J, Barr AR, Whitby MC. 2005. The F-Box DNA helicase Fbh1 prevents Rhp51-dependent recombination without mediator proteins. Mol Cell Biol 25:8084–8096.

Otsuki M, Seki M, Inoue E, Abe T, Narita Y, Yoshimura A, Tada S, Ishii Y, Enomoto T. 2007. Analyses of functional interaction between RECQL1, RECQL5, and BLM which physically interact with DNA topoisomerase IIIalpha. Biochim Biophys Acta 1782:75–81.

Pichierri P, Franchitto A, Rosselli F. 2004. BLM and the FANC proteins collaborate in a common pathway in response to stalled replication forks. EMBO J 23:3154–3163.

Pickford A, Braccini L, Macino G, Cogoni C. 2003. The QDE-3 homologue RecQ-2 co-operates with QDE-3 in DNA repair in Neurospora crassa. Curr Genet 42:220–227.

Powell SN, Kachnic LA. 2008. Therapeutic exploitation of tumor cell defects in homologous recombination. Anticancer Agents Med Chem 8: 448–460.

Sakamoto-Hojo ET, Balajee AS. 2008. Targeting poly (ADP) ribose polymerase I (PARP-1) and PARP-1 interacting proteins for cancer treatment. Anticancer Agents Med Chem 8:402–416.

Sharma S, Sommers JA, Driscoll HC, Uzdilla L, Wilson TM, Brosh RM, Jr. 2003a. The exonucleolytic and endonucleolytic cleavage activities of human Exonuclease 1 are stimulated by an interaction with the carboxyl-terminal region of the Werner syndrome protein. J Biol Chem 278:23487–23496.

Sharma S, Sommers JA, Wu L, Bohr VA, Hickson ID, Brosh RM, Jr. 2003b. Stimulation of flap endonuclease-1 by the Bloom's syndrome protein. J Biol Chem 279:9847–9856.

Sharma S, Otterlei M, Sommers JA, Driscoll HC, Dianov GL, Kao HI, Bambara RA, Brosh RM, Jr. 2004a. WRN helicase and FEN-1 form a complex upon replication arrest and together process branch-migrating DNA structures associated with the replication fork. Mol Biol Cell 15:734–750.

Sharma S, Sommers JA, Brosh RM, Jr. 2004b. In vivo function of the conserved non-catalytic domain of Werner syndrome helicase in DNA replication. Hum Mol Genet 13:2247–2261.

Sharma S, Sommers JA, Brosh RM, Jr. 2008. Processing of DNA replication and repair intermediates by the concerted action of RecQ helicases and Rad2 structure-specific nucleases. Protein Pept Lett 15:89–102.

Trowbridge K, McKim K, Brill SJ, Sekelsky J. 2007. Synthetic lethality of Drosophila in the absence of the MUS81 endonuclease and the DmBlm helicase is associated with elevated apoptosis. Genetics 176:1993–2001.

Wang W. 2007. Emergence of a DNA-damage response network consisting of Fanconi anaemia and BRCA proteins. Nat Rev Genet 8:735–748.

Wang W, Seki M, Narita Y, Sonoda E, Takeda S, Yamada K, Masuko T, Katada T, Enomoto T. 2000. Possible association of BLM in decreasing DNA double strand breaks during DNA replication. EMBO J 19:3428–3435.

Wang W, Seki M, Narita Y, Nakagawa T, Yoshimura A, Otsuki M, Kawabe Y, Tada S, Yagi H, Ishii Y, Enomoto T. 2003. Functional relation among RecQ family helicases RecQL1, RecQL5, and BLM in cell growth and sister chromatid exchange formation. Mol Cell Biol 23:3527–3535.

Zhang R, Sengupta S, Yang Q, Linke SP, Yanaihara N, Bradsher J, Blais V, McGowan CH, Harris CC. 2005. BLM helicase facilitates Mus81 endonuclease activity in human cells. Cancer Res 65:2526–2531.