Role of DNA Mismatch Repair in the Cytotoxicity of Ionizing Radiation[1]

James A. Fritzell, Latha Narayanan, Sean M. Baker, C. Eric Bronner, Susan E. Andrew, Tomas A. Prolla, Allan Bradley, Frank R. Jirik, R. Michael Liskay, and Peter M. Glazer[2]

Departments of Therapeutic Radiology and Genetics, Yale University School of Medicine, New Haven, Connecticut 06520-8040 [J. A. F., L. N., P. M. G.]; Department of Molecular and Medical Genetics, Oregon Health Sciences University, Portland, Oregon 97201-3098 [S. M. B., C. E. B., R. M. L]; Centre for Molecular Medicine and Therapeutics and Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z3 [S. E. A., F. R. J.]; and Howard Hughes Medical Institute and Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030 [T. A. P., A. B.]

ABSTRACT

The DNA mismatch repair (MMR) system in mammalian cells not only serves to correct base mispairs and other replication errors, but it also influences the cellular response to certain forms of DNA damage. Cells that are deficient in MMR are relatively resistant to alkylation damage because, in wild-type cells, the MMR system is thought to promote toxicity via futile repair of alkylated mispairs. Conversely, MMR-deficient cells are sensitive to UV light, possibly due to the requirement for MMR factors in transcription-coupled repair of active genes. MMR deficiency has been associated with familial and sporadic carcinomas of the colon and other sites, and so, we sought to determine the influence of MMR status on cellular response to ionizing radiation, an agent commonly used for cancer therapy. Fibroblast cell lines were established from transgenic mice carrying targeted disruptions of one of three MMR genes in mammalian cells: Pms2, Mlh1, or Msh2. In comparison to wild-type cell lines from related mice, the Pms2-, Mlh1-, or Msh2-nullizygous cell lines were found to exhibit higher levels of clonogenic survival following exposure to ionizing radiation. Because ionizing radiation generates a variety of lesions in DNA, the differences in survival may reflect a role for MMR in processing a subset of these lesions, such as damaged bases. These results both identify a new class of DNA-damaging agents whose effects are modulated by the MMR system and may help to elucidate pathways of radiation response in cancer cells.

INTRODUCTION

Correction of replication errors is critical for the maintenance of genomic integrity. In mammalian cells, several homologues of the *Escherichia coli* MutL and MutS proteins have been identified, and these appear to play a role in postreplicative DNA MMR[3] (1, 2). In humans, mutations in the MMR genes *MSH2*, *MLH1*, *PMS2*, and *PMS1* have been linked to hereditary carcinoma of the colon and of other sites (1, 2). Some fraction of sporadic cancers may also show MMR deficiency (3). Transgenic mice with targeted disruptions of selected MMR genes are cancer prone and have spontaneous mutation frequencies that are up to 100-fold elevated above that of the wild type (4–7).[4]

However, evidence is accumulating that the activities of the MMR factors are not limited to mismatch correction. Mice lacking Pms2 or Mlh1 function show specific patterns of infertility (4, 5), suggesting a role for these factors in meiosis. Mellon *et al.* (8) have demonstrated

that human cancer cells that are deficient in MMR exhibit slower-than-normal removal of UV damage from the transcribed strand of active genes, implying that efficient transcription-coupled repair, in some manner, requires the MMR system. It was also found that MMR-deficient cells exhibit mildly decreased survival following UV irradiation (8). In contrast, cells that are deficient in MMR demonstrate significantly increased survival relative to the wild type upon exposure to alkylating agents (9, 10). This alkylation tolerance in cells lacking MMR is thought to reflect a role for MMR in mediating the toxicity of alkylation damage. By one model, the MMR pathway may recognize mispairs formed during replication of an alkylated template. The system initiates futile attempts to repair the undamaged daughter strand, leading to excessive strand breaks and consequent lethality (9–12). Cells without active MMR do not attempt this abortive repair and are spared the full toxic effects of alkylation damage. Therefore, the MMR system in mammalian cells can influence the cellular response to a variety of lesions other than mismatches, and it appears to participate in multiple repair pathways.

We sought to determine whether the MMR system might have a role in the processing of X-ray damage, thereby influencing radiation cytotoxicity. Ionizing radiation induces a large variety of lesions in DNA, including not only strand breaks but also base damage and sugar damage (13, 14). Because of the complexity of radiolytic products in DNA, the role of MMR in the cellular radiation response was not readily predictable. However, we hypothesized that the MMR system might recognize and process mispairs, resulting from some forms of oxidative base damage, in a fashion analogous to the alkylation damage response. If so, the cytotoxicity of such damage would depend on MMR, and therefore, MMR function would be responsible for some proportion of radiation-induced cell death.

We had previously reported analyses of tumorigenesis, fertility, and mutagenesis in transgenic mice with targeted disruptions of the *Pms2*, *Mlh1*, and *Msh2* genes (4–7). Pms2 and Mlh1 are MutL homologues in the mammalian MMR complex, whereas Msh2 is one of the several MutS homologues (1, 2). Using immortalized cell lines established from these mice, we evaluated radiation cytotoxicity as a function of MMR status. We report here that mouse cells that are deficient in *Pms2*, *Mlh1*, or *Msh2* show increased clonogenic survival relative to wild-type cells following exposure to ionizing radiation, suggesting that a measurable component of radiation cytotoxicity is mediated by MMR activity.

MATERIALS AND METHODS

Cells. Mouse fibroblast cell lines, 40wt and 29pms2, were established from littermate newborn mice as described (15). Transformation was carried out by transfection with an SV40 T antigen-expressing vector, as described (15). Lines BC1 and MS5–7 msh2 were derived from 13-day mouse embryos and were also established by SV40 T-antigen transfection. Briefly, the embryos were minced, trypsinized, and explanted into MEM supplemented with 15% FCS. Embryo genotypes were determined by PCR analysis (7), and samples were chosen for immortalization. Cells (5×10^5) were transfected by calcium phosphate coprecipitation with 10 μg of SV40 plasmid, 1 μg of pc1neo plasmid, and 10 μg of salmon sperm DNA as carrier. The medium was changed the following day, and the cells were selected in 200 μg/ml G418.

Table 1 *Mismatch repair-deficient fibroblast cell lines established from transgenic mice*

Cell line	Genotype	Method of immortalization
29pms2	*Pms2 −/−*	SV40 T antigen
C18pms2	*Pms2 −/−*	Growth through crisis
MC2mlh1	*Mlh1 −/−*	Growth through crisis
MS5-7 msh2	*Msh2 −/−*	SV40 T antigen
40wt	Wild type	SV40 T antigen
BC1wt	Wild type	SV40 T antigen

Transfectant clones were isolated 12–14 days later as foci of morphologically transformed cells. Clones were used for experiments at early passage (less than 5), but an aliquot of each clone was serially passaged to confirm immortalization. The fibroblast cell lines MC2mlh1 and C18pms2 were derived from mouse embryos, and immortalized clones were isolated by growth through crisis, with cells being split 1:3 every 3–4 days. The characteristics of the cell lines are summarized in Table 1. Cell genotypes were confirmed by PCR amplification of the *Pms2, Mlh1,* and *Msh2* loci to detect the presence or absence of the targeted disruption, as described previously (4–7). Established cell lines were grown in DMEM supplemented with 10% FCS and 2× amino acids, 2× vitamins, 2× nonessential amino acids, penicillin, and streptomycin (Life Technologies, Inc., Bethesda, MD).

Clonogenic Survival Assays. The mouse cells were seeded into 100 × 20 mm dishes by serial dilutions and were exposed to MNU, UV light, or ionizing radiation, as indicated. MNU (Sigma Chemical Co., St. Louis, MO) was diluted in DMEM from a 1 M stock solution and applied to the cell monolayers, yielding concentrations from 0 to 3 mM, in 0.5 mM increments. MNU expo-

sures were carried out for 30 min at 37°C, after which the cells were washed, and fresh growth medium was added. UV irradiation was performed using a 254-nm germicidal lamp, with cells irradiated in the absence of growth medium at doses ranging from 0 to 18 J/m^2. Growth medium was replaced immediately afterward. For X-ray treatments, cells were irradiated using a ^{137}Cs irradiator at a dose rate of 225 rad/min in growth medium. Doses ranging from 0 to 1200 rad were given. Surviving colonies were fixed and stained with crystal violet for visualization after 10 days in culture. For each experiment, two replicate dishes were examined at each dose, and only those colonies containing 50 or more cells were scored as surviving clones. After normalization for the plating efficiencies of the cell lines, the fractional survival was determined at each dose. Each experiment was repeated several times, as indicated in the text. Error bars were generated by calculation of the SE for the results of the multiple experiments.

RESULTS

MMR-deficient Cell Lines. To test the influence of MMR on radiation cytotoxicity, we established cell lines with defined genotypes at selected MMR gene loci (Table 1). We had previously established transgenic mice carrying targeted disruptions of either the *Pms2* or *Mlh1* genes (4–6). Mice that were deficient in *Msh2* were obtained from Reitmair and colleagues (7, 16). From heterozygote-by-heterozygote crosses, we generated mouse embryos or newborn mice nullizygous for *Pms2, Mlh1,* or *Msh2,* along with the wild type. Embryonic tissue was genotyped by PCR amplification of sequences within the loci in question, as described previously (4–7), and fibro-
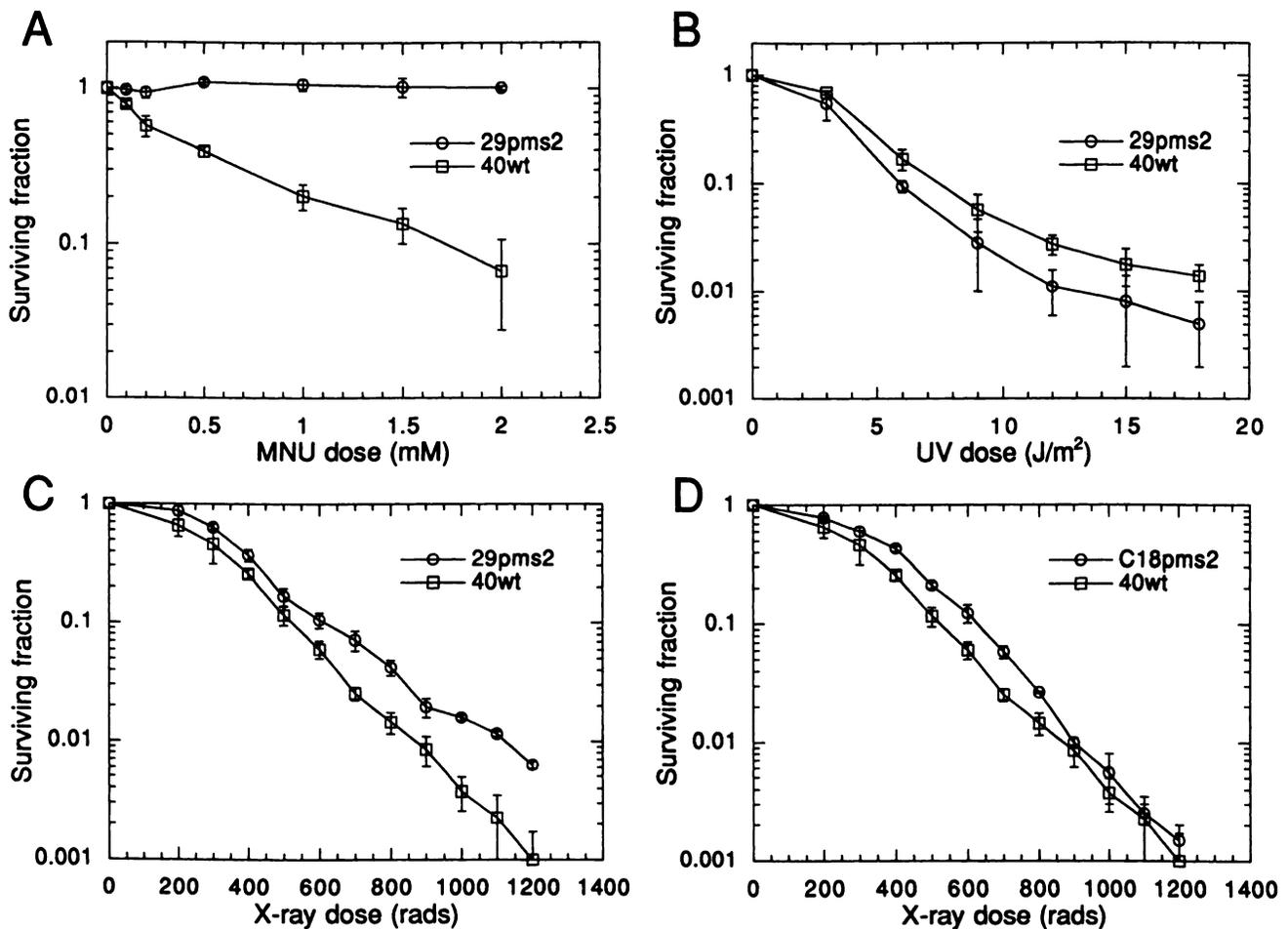

Fig. 1. Cytotoxicity of MNU (*A*), UV (*B*), and ionizing radiation (*C* and *D*) in wild-type and Pms2-deficient mouse cells. *A,* clonogenic survival of 40wt (wild type) and 29pms2 (*Pms2* nullizygous) cells following exposure to the alkylating agent, MNU. *B,* survival of 40wt and 29pms2 cells following UV irradiation. *C,* survival of 40wt and 29pms2 following ionizing radiation. *D,* survival of 40wt and C18pms2 (a second *Pms2*-nullizygous cell line) following ionizing radiation. *Data points,* means for the following number of independent experiments: *A,* four; *B,* three; *C,* five; *D,* four. *Bars,* SE.
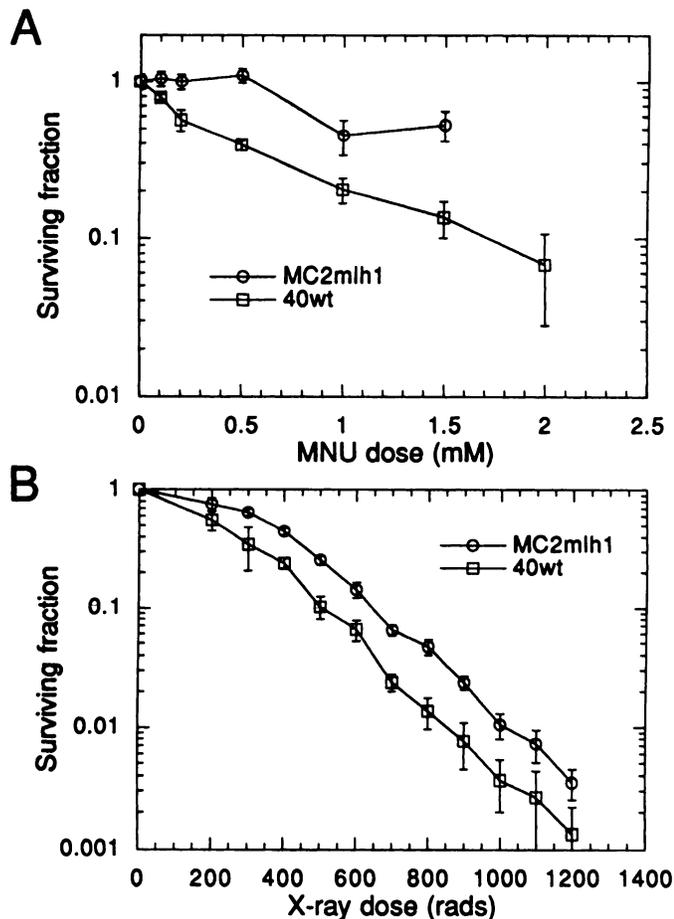
5144

Fig. 2. Cytotoxicity of MNU (*A*) and ionizing radiation (*B*) in wild-type and Mlh1-deficient mouse cells. *A*, clonogenic survival of 40wt (wild type) and MC2mlh1 (*Mlh1* nullizygous) cells following exposure to MNU. *B*, survival of 40wt and MC2mlh1 cells following ionizing irradiation. Data points, means for the following number of independent experiments: *A*, two; *B*, four. *Bars*, SE.

blast cultures were established from selected embryos. Permanent cell lines were established in one of two ways. The 40wt (wild type), BC1wt (wild type), 29pms2 (*Pms2* nullizygous), and MS5–7 msh2 (*Msh2* nullizygous) cell lines were generated following transfection of the explanted fibroblasts with a vector expressing SV40 T antigen. The C18pms2 (*Pms2* nullizygous) and MC2mlh1 (*Mlh1* nullizygous) cell lines were established by serial passage of the respective cells through crisis.

MNU and UV Response in Pms2-deficient Cells. Before examining X-ray cytotoxicity, we asked whether the mouse cell lines would display the same alkylation tolerance and UV sensitivity that have been reported for human tumor cell lines (8–10). Clonogenic assays for cell survival following MNU and UV treatment were performed. The MMR-deficient 29pms2 cells showed better survival following MNU exposure than did the wild-type 40wt cells (Fig. 1*A*), consistent with previous reports of alkylation tolerance in human MMR-deficient cells (9, 10). The response of the cells to UV light is shown in Fig. 1*B*. In keeping with the results of Mellon *et al.* (8), the 29pms2 cells were slightly sensitive to UV, presumably reflecting the importance of transcription-coupled excision repair in cell survival after UV damage. These experiments demonstrate that the Pms2-deficient mouse fibroblasts have the alkylation-tolerant and UV-sensitive phenotypes that are expected for MMR-deficient cells.

Radioresistance of *Pms2*-nullizygous Cells. We next tested cell survival following exposure to ionizing radiation. The 29pms2

cells showed higher levels of clonogenic survival than did the 40wt cells (Fig. 1*C*). The combined data of five independent experiments are shown, with the SE indicated. To confirm that this finding reflects the influence of Pms2 deficiency and is not a peculiarity of the 29pms2 line, we also tested another, independently derived *Pms2*-nullizygous fibroblast line, C18pms2 (Fig. 1*D*). This cell line was established from the same lineage of *Pms2* knockout mice, but in a different laboratory and by a different method (Table 1). Again, the Pms2-deficient cells showed a small but measurable difference in radioresistance. Although the differential radiation tolerance of the *Pms2*-nullizygous cells (Fig. 1, *C* and *D*) is not as striking as their alkylation tolerance (Fig. 1*A*), the absence of MMR clearly confers some level of radiation resistance, implying that a fraction of the radiation cytotoxicity in wild-type cells is dependent on Pms2 function.

Mlh1- and *Msh2*-nullizygous Cells. To further correlate radiation response with MMR activity, we also tested cells that were nullizygous for *Mlh1*, another *mutL* homologue in mammalian cells, and for *Msh2*, one of the *mutS* homologues. Like mutations in the human *PMS2* gene, mutations in the human *MLH1* and *MSH2* genes are linked to hereditary colon cancer (1, 2). As shown in Fig. 2*A*, the Mlh1-deficient cell line, MC2mlh1, displayed the expected alkylation tolerance upon MNU exposure. Following ionizing radiation (Fig. 2*B*), the MC2mlh1 cells also showed better survival than did the wild-type cells, to an extent similar to that seen with the Pms2-

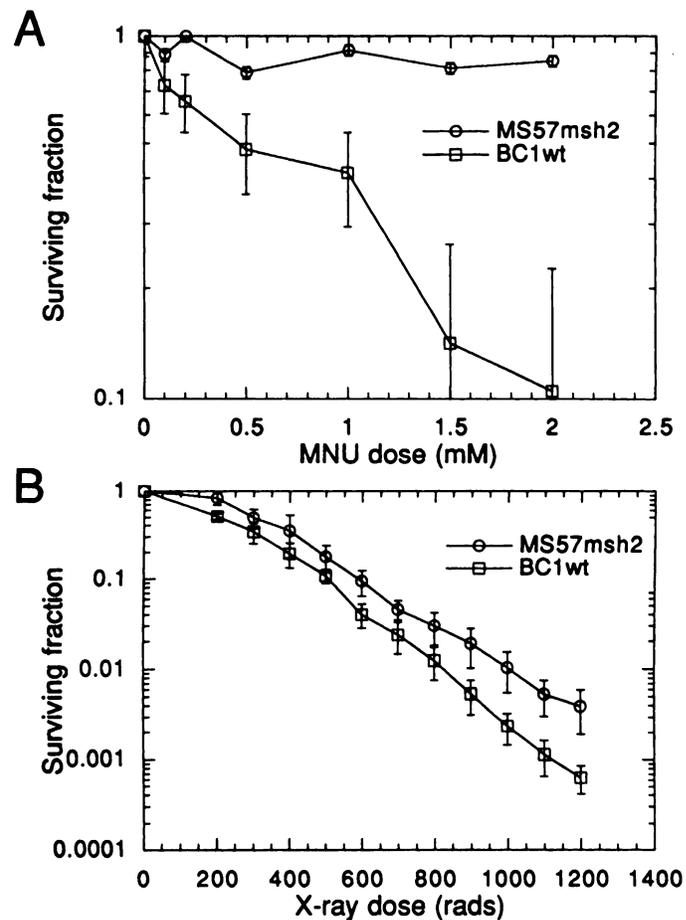Fig. 3. Cytotoxicity of MNU (*A*) and ionizing radiation (*B*) in wild-type and Msh2-deficient mouse cells. *A*, clonogenic survival of BC1wt (wild type) and MS5–7 msh2 (*Msh2* nullizygous) cells following exposure to MNU. *B*, survival of BC1wt and MS5–7 msh2 cells following ionizing irradiation. Data points, means for the following number of independent experiments: *A*, two; *B*, five. *Bars*, SE.

5145

deficient cells (Fig. 1, C and D). The Msh2-nullizygous cells (MS5–7 msh2) were compared to a different wild-type line (BC1wt; Fig. 3). As with the Pms2 and Mlh1 null cells, the MS5–7 msh2 cells showed a high level of MNU resistance (Fig. 3A) and a low but detectable level of radiation resistance (Fig. 3B).

DISCUSSION

We have examined X-ray cytotoxicity in fibroblast cell lines established from transgenic mice carrying targeted disruptions of selected DNA MMR genes. Cells nullizygous for Pms2, Mlh1, and Msh2 were compared to the wild type, and in all cases, the MMR-deficient cells exhibited higher levels of clonogenic survival following irradiation than did the wild type. The differences in X-ray survival versus the wild-type lines were small, but they were detectable and statistically significant (based on SE calculations for the results of multiple independent experiments).

This work was performed using cell lines established from wild-type and knockout mice that were deficient in MMR. The use of such lines is advantageous because the genotypes of the cell lines are well defined and because such newborn- or embryo-derived lines are fairly close to being otherwise "normal," with regard to other aspects of cell physiology. However, one major caveat is that the property in question, MMR deficiency, confers a strong mutator phenotype (6, 7). Hence, during establishment and growth of the cells in culture, some accumulation of other genetic defects is possible. To address this problem, we examined several different MMR-deficient cell lines, reasoning that such potentially confounding secondary mutations would likely vary among independently generated lines. We tested two independently derived Pms2-nullizygous lines established by different methods, as well as Mlh1- and Msh2-nullizygous lines. The consistent results obtained with all four lines suggest that the observed differences can be attributed to MMR deficiency.

In human cancer cell lines, MMR-deficiency has been previously associated with resistance to simple alkylating agents (9, 10), such as MNU. MMR-deficient cancer cells have also been shown to be resistant to cis-platinum (17–19), an antineoplastic agent in widespread clinical use. The mechanism for this resistance has not yet been established. However, the human MutSα complex (a heterodimer of MSH2 and MSH6) can recognize and bind in vitro to damaged base pairs containing O^6-methylguanine, O^4-methylthymine, the cisplatin-d(GpG) adduct, and aminofluorene adducts (20–22). These results support a model in which the MMR system acts on mismatches generated by replication of alkylated DNA (e.g., O^6-methyl-G:T mispairs; Ref. 12). Efforts to repair the daughter strand are futile because the lesion remains in the parent strand and the complex mismatch is regenerated by repair synthesis. Such abortive repair may initiate a pathway leading to lethality, perhaps via the production of excessive strand breaks.

Because ionizing radiation generates a wide variety of lesions in DNA, a certain subset of these lesions may constitute substrates for futile MMR activity. X-ray damage to cellular DNA includes single- and double-strand breaks, base damage, and sugar damage (13). A common base lesion in irradiated DNA is 8-oxo-G, which is known to mispair with A (23). Following replication of X-ray damaged DNA, such a mismatch might provoke abortive MMR and cell death, in a manner consistent with the model for alkylation damage.

On the other hand, transcription-coupled repair of ionizing radiation damage has been demonstrated (24, 25), and MMR proteins may turn out to have some role in this process, as in the case of UV damage. If so, MMR deficiency might confer some degree of radiation sensitivity due to diminished repair. However, our observation of radiation

resistance in MMR-deficient cells suggests that this effect, if present, is small and is overshadowed by the the damage tolerance mechanism described above.

Nonetheless, much of the damage produced by X-rays is in the form of direct strand breaks (13), and the lethality of these lesions is unlikely to depend on MMR activity. In fact, the data presented here indicate that most of the cytotoxicity of ionizing radiation is independent of the MMR status of the cells. At a dose of 1000 rad, there is still approximately 99% cell death in the MMR-deficient cells.

Comparison of our results with the data of Fink et al. (17) regarding the influence of MMR on cis-platinum cytotoxicity reveals that MMR plays a significantly greater role in the case of cis-platinum than it does in the case of ionizing radiation. Fink et al. (17) used fibroblasts established from Msh2 knockout and wild-type mice, and so, their results are comparable to our analysis of Msh2-deficient cells presented in Fig. 3. (They did not, however, use the same Msh2 knockout mouse lineage.) At doses of X-rays and cis-platinum that yielded 10% survival in the wild-type cells, the Msh2-deficient cells showed approximately 18% survival after X-ray treatment (our data; Fig. 3), but they showed 40% survival following cis-platinum exposure (Ref. 17; Fig. 2).

Although the influence of MMR on radiation toxicity is, therefore, small, our findings may have clinical significance. Over the course of a typical cancer treatment regimen of up to 30–35 doses of 200 rad each, a small difference in radiation response with each dose could theoretically lead to a significant impact on the probability of tumor control. At this point, however, the work presented here should not be interpreted to mean that tumors with MMR deficiency are necessarily more radioresistant than are other tumors. Many factors can influence radiation resistance (26), and most tumors have derangements of multiple cellular pathways, some of which may promote resistance while others may cause sensitivity. Hence, although our results identify MMR as a pathway that may contribute to cellular radiation response, caution must be used at this time in extrapolating to clinical situations.

ACKNOWLEDGMENTS

REFERENCES

1. Modrich, P., and Lahue, R. Mismatch repair in replication fidelity, genetic recombination, and cancer biology. Annu. Rev. Biochem., 65: 101–133, 1996.
2. Kolodner, R. Biochemistry and genetics of eukaryotic mismatch repair. Genes Dev., 10: 1433–1442, 1996.
3. Kane, M. F., Loda, M., Gaida, G. M., Lipman, J., Mishra, R., Goldman, H., Jessup, J. M., and Kolodner, R. Methylation of the hMLH1 promoter correlates with lack of expression of hMLH1 in sporadic colon tumors and mismatch repair-defective human tumor cell lines. Cancer Res., 57: 808–811, 1997.
4. Baker, S. M., Bronner, C. E., Zhang, L., Plug, A. W., Robatzek, M., Warren, G., Elliott, E. A., Yu, J., Ashley, T., Arnheim, N., Flavell, R. A., and Liskay, R. M. Male mice defective in the DNA mismatch repair gene PMS2 exhibit abnormal chromosome synapsis in meiosis. Cell, 82: 309–319, 1995.
5. Baker, S. M., Plug, A. W., Prolla, T. A., Bronner, C. E., Harris, A. C., Yao, X., Christie, D. M., Monell, C., Arnheim, N., Bradley, A., Ashley, T., and Liskay, R. M. Involvement of mouse Mlh1 in DNA mismatch repair and meiotic crossing over. Nat. Genet., 13: 336–342, 1996.
6. Narayanan, L., Fritzell, J. A., Baker, S. M., Liskay, R. M., and Glazer, P. M. Elevated levels of mutation in multiple tissues of mice deficient in the DNA mismatch repair gene, Pms2. Proc. Natl. Acad. Sci. USA, 94: 3122–3127, 1997.
7. Andrew, S. E., Reitmar, A. H., Fox, J., Hsiao, L., Francis, A., Mckinnon, M., Mak, T. W., and Jirik, F. Base transitions dominate the mutational spectrum of a transgenic reporter gene in MSH2 deficient mice. Oncogene, 15: 123–129, 1997.
8. Mellon, I., Rajpal, D. K., Koi, M., Boland, C. R., and Champe, G. N. Transcription-coupled repair deficiency and mutations in human mismatch repair genes. Science (Washington DC), 272: 557–560, 1996.
9. Branch, P., Aquilina, G., Bignami, M., and Karran, P. Defective mismatch binding and a mutator phenotype in cells tolerant to DNA damage. Nature (Lond.), 362: 652–654, 1993.
10. Kat, A., Thilly, W. G., Fang, W. H., Longley, M. J., Li, G. M., and Modrich, P. An

5146

alkylation-tolerant, mutator human cell line is deficient in strand-specific mismatch repair. Proc. Natl. Acad. Sci. USA, *90:* 6424–6428, 1993.

11. Drummond, J. T., Anthoney, A., Brown, R., and Modrich, P. Cisplatin and adriamycin resistance are associated with MutLα and mismatch repair deficiency in an ovarian tumor cell line. J. Biol. Chem., *271:* 19645–19648, 1996.

12. Karran, P., and Marinus, M. G. Mismatch correction at O^6-methylguanine residues in *E. coli* DNA. Nature (Lond.), *296:* 868–869, 1982.

13. Hutchinson, F. Chemical changes induced in DNA by ionizing radiation. Prog. Nucleic Acid Res. Mol. Biol., *32:* 115–154, 1985.

14. Ward, J. F. DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability. Prog. Nucleic Acid Res. Mol. Biol., *35:* 95–125, 1988.

15. Leach, E. G., Gunther, E. J., Yeasky, T. M., Gibson, L. H., Yang-Feng, T. L., and Glazer, P. M. Frequent spontaneous deletions at a shuttle vector locus in transgenic mice. Mutagenesis, *11:* 49–56, 1996.

16. Reitmair, A. H., Schmits, R., Ewel, A., Bapat, B., Redston, M., Mitri, A., Waterhouse, P., Mittrucker, H. W., Wakeham, A., Liu, B., Thomasun, A., Griesser, H., Gallinger, S., Ballhausen, N. G., Fishel, R., and Mak, T. W. MSH2 deficient mice are viable and susceptible to lymphoid tumours. Nat. Genet., *11:* 64–70, 1995.

17. Fink, D., Nebel, S., Aebi, S., Zheng, H., Cenni, B., Nehme, A., Christen, R. D., and Howell, S. B. The role of DNA mismatch repair in platinum drug resistance. Cancer Res., *56:* 4881–4886, 1996.

18. Fink, D., Zheng, H., Nebel, S., Norris, P. S., Aebi, S., Lin, T. P., Nehme, A., Christen, R. D., Haas, M., MacLeod, C. L., and Howell, S. B. *In vitro* and *in vivo* resistance to cisplatin in cells that have lost DNA mismatch repair. Cancer Res., *57:* 1841–1845, 1997.

19. Aebi, S., Kurdi-Haidar, B., Gordon, R., Cenni, B., Zheng, H., Fink, D., Christen, R. D., Boland, C. R., Koi, M., Fishel, R., and Howell, S. B. Loss of DNA mismatch repair in acquired resistance to cisplatin. Cancer Res., *56:* 3087–3090, 1996.

20. Duckett, D. R., Drummond, J. T., Murchie, A. I. H., Reardon, J. T., Sancar, A., Lilley, D. M. J., and Modrich, P. Human MutSα recognizes damaged DNA base pairs containing O^6-methylguanine, O^4-methylthymine, or the cisplatin-d(GpG) adduct. Proc. Natl. Acad. Sci. USA, *93:* 6443–6447, 1996.

21. Mello, J. A., Acharya, S., Fishel, R., and Essigmann, J. M. The mismatch-repair protein hMSH2 binds selectively to DNA adducts of the anticancer drug cisplatin. Chem. Biol., *3:* 579–589, 1996.

22. Li, G. M., Wang, H., and Romano, L. J. Human MutSα specifically binds to DNA containing aminofluorene and acetylaminofluorene adducts. J. Biol. Chem., *271:* 24084–24088, 1996.

23. Shibutani, S., Takeshita, M., and Grollman, A. P. Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxo-dG. Nature (Lond.), *349:* 431–434, 1991.

24. Leadon, S. A., and Cooper, P. K. Preferential repair of ionizing radiation-induced damage in the transcribed strand of an active human gene is defective in Cockayne syndrome. Proc. Natl. Acad. Sci. USA, *90:* 10499–10503, 1993.

25. Cooper, P. K., Nouspikel, T., Clarkson, S. G., and Leadon, S. A. Defective transcription-coupled repair of oxidative base damage in Cockayne syndrome patients from XP group G. Science (Washington DC), *275:* 990–993, 1997.

26. Maity, A., Kao, G. D., Muschel, R. J., and McKenna, W. G. Potential molecular targets for manipulating the radiation response. Int. J. Radiat. Oncol. Biol. Phys., *37:* 639–653, 1997.

Role of DNA Mismatch Repair in the Cytotoxicity of Ionizing Radiation

James A. Fritzell, Latha Narayanan, Sean M. Baker, et al.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/57/22/5143	

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, use this link http://cancerres.aacrjournals.org/content/57/22/5143. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.	