Suppression of DNA Repair by Human T Cell Leukemia Virus Type 1 Tax Is Rescued by a Functional p53 Signaling Pathway*

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The tax protein of human T cell leukemia virus type 1 is a viral transactivator and transforming protein. Tax is known to suppress cellular nucleotide excision repair (NER), and this activity has been proposed to play an important role in Tax transformation. In this study we have investigated the mechanism by which Tax suppresses NER with specific focus on the previously characterized ability of Tax to inhibit p53 function. Suppression of NER by Tax was rescued by overexpression of wild-type p53; however, a p53 transactivation-incompetent mutant did not restore NER activity. The cyclin-dependent kinase inhibitor p21, a major transcriptional target of p53, plays an important role in regulating DNA replication and repair. Overexpression of p21 reversed Tax-induced suppression of NER; however, a p21 C-terminal mutant that lacks the proliferating cell nuclear antigen binding domain did not restore NER activity. Thus, p53 and its downstream effector p21 can inhibit Tax-mediated suppression of DNA repair. These results imply that the inactivation of p53 function by Tax contributes to Tax suppression of DNA repair.

Human T cell leukemia virus type 1 (HTLV-1) is the etiological agent of adult T cell leukemia (ATL) (1), and a neurodegenerative disease, known as tropical spastic paraparesis or HTLV-1-associated myelopathy (2). ATL develops in less than 5% of HTLV-1-infected individuals after a long clinical latency of several decades. Cytogenetic studies of leukemic cells from ATL patients and HTLV-1-immortalized lymphocytes have identified diverse chromosomal abnormalities (reviewed in Ref. 3). Although such chromosomal changes are common in HTLV-1-transformed cells, no consistent abnormalities have been found in all ATL patients (3). In combination with this genetic damage, the long latency associated with HTLV-1-induced leukemogenesis and the small percentage of infected individuals who develop ATL suggest that an accumulation of DNA damage induced by a generalized dysregulation of host DNA replication or repair contributes to neoplastic transformation.

The accumulation of DNA damage in HTLV-1-transformed cells has been associated with expression of the viral gene, tax. Cells expressing HTLV-1 Tax display an increased frequency of micronuclei formation (4, 5) that typically results from chromosomal damage. In addition, Tax expression has been associated with an increased mutation frequency of the cellular genome (6). The ability of Tax to suppress cellular DNA repair may provide the basis for both of these effects. Tax represses expression of human β-polymerase (7), an important enzyme involved in base excision repair, suggesting that Tax may interfere with this DNA repair pathway. Recently, Tax has been shown to suppress directly both nucleotide excision repair (NER) and base excision repair (8, 9), further supporting a role for Tax in the genome instability observed in HTLV-1-infected cells.

Tax is an activator of viral and cellular transcription and has been shown to transactivate the human proliferating cell nuclear antigen (PCNA) promoter (10). The ability of Tax to suppress NER correlates with its ability to activate PCNA gene expression (8). PCNA, an essential protein expressed in all proliferating eukaryotic cells, is a cofactor of DNA polymerase δ and plays crucial roles in DNA replication, DNA repair, and chromatin assembly (for review, see Ref. 11). The effect of PCNA on DNA replication and repair is coupled through a complex pathway involving cyclins, cyclin-dependent kinases (cdks), and p21. PCNA can directly bind to cyclin D1 and p21 (12, 13) and can exist as a complex with cyclin D/cdk4/p21, cyclinA/cdk2/p21, or cyclin E/cdk2/p21 (14).

p21 (Cip1, Waf1, and Sdi1), a potent inhibitor of cdk activity whose expression is regulated by p53 (15, 16), is an important regulator of cellular DNA repair and cell cycle progression. Following DNA damage, p21 expression is activated by p53. p21 then associates with PCNA and inhibits the ability of PCNA to stimulate DNA replication without interfering with PCNA-dependent DNA repair (17, 18). The stoichiometry of the p21-PCNA complex is important, as overexpression of PCNA promotes nucleotide misincorporation as well as incorporation of a nucleotide analog by polymerase δ (19, 20). Thus, excess PCNA appears to overcome the p21 block of DNA replication, thereby allowing DNA polymerase δ synthesis past template lesions and promoting the introduction of non-template mutations.

p53 is an important regulator of cellular genome stability and an inducer of apoptotic cell death. Loss or inactivation of p53 has been causally associated with oncogenic transformation (21). Mutations within the p53 gene in HTLV-1-transformed cells are not observed as frequently as in other types of tumors (22) suggesting that p53 may be inactivated by alternative means during HTLV-1 transformation. Tax can inactivate p53 through several pathways, including repression of p53 transcription (23) and inactivation of p53 transactivation abil-
ity (22, 24–26). Inactivation of p53 function by Tax occurs by inducing p53 phosphorylation (27), competition for CBP binding (28), and/or by stabilizing p53 protein (24, 29, 30).

We previously demonstrated that overexpression of PCNA induced by Tax inhibited DNA repair and allowed DNA replication in the presence of DNA damage (8, 31). In this report, we investigated the role of p53 in the suppression of DNA repair by Tax. The results demonstrated that p53 and its downstream target, p21, can both rescue Tax-mediated suppression of NER. Thus, the ability of Tax to inhibit p53 function and its ability to activate PCNA gene expression both contribute to Tax suppression of NER.

**Experimental Procedures**

**Plasmids and Cells**—pCMV-Tax, pMSV-Luc, and pcDNA-PCNA have been described previously (10). pCMVp21<sup>SDI1/HA</sup> is an HA-tagged wild-type p21 expression vector, and pCMVp21<sup>DM/HA</sup> (142–147) is an HA-tagged p21 expression vector containing a deletion mutation in the PCNA binding domain. Both p21 plasmids were received from James Smiley (Baylor College of Medicine) (32) and are designated here as wt p21 and mt p21, respectively. p53-LTRA and p53-LTRV are wild-type and mutant p53 expression vectors, respectively. Both p53 plasmids were received from G. Lozano (M.D. Anderson Cancer Center, University of Texas Health Science Center, Houston) (33), and are designated here as wt p53 and mt p53, respectively. The luciferase reporter, pG13pyLuc, contains 13 copies of a consensus p53-responsive element and was provided by John Brady (NCI, National Institutes of Health).

CREF cell lines have been described previously (8). Wild-type and p53-deficient mouse fibroblast cells were received from L. A. Donehower (Baylor College of Medicine) (34).

**Antibodies and Immunoblot Analysis**—One million cells were lysed in 1 ml of SDS sample buffer. Fifty microfilters of the lysates were electrophoresed in a 10% SDS-polyacrylamide gel. The proteins were electroblotted onto a polyvinylidene fluoride membrane (Immobilon-P, Millipore) and probed with either an anti-β-actin monoclonal antibody (12CA5, Roche Molecular Biochemicals), an anti-PCNA monoclonal antibody (PC-10, Santa Cruz Biotechnology), an anti-Tax polyclonal antibody (12CA5, Roche Molecular Biochemicals), or an anti-p53 polyclonal antibody (Ab-7, Oncogene Science). Immunoreactivity was detected with an enhanced chemiluminescence detection kit (ECL, Amersham Pharmacia Biotech). The expression of α-actin was used as an internal loading control and was detected using an anti-actin monoclonal antibody (20–33, Sigma).

**Cell Cycle Distribution Assays**—Asynchronously growing CREF-Neo and CREF-Tax cells were trypsinized, and 1 × 10<sup>6</sup> cells were washed with phosphate-buffered saline and then resuspended in 2 ml of 0.9% NaCl. The cells were fixed in 5 ml of 95% ethanol. DNA content was analyzed by staining with propidium iodide (50 μg/ml) and RNase A treatment, followed by flow cytometric analysis (Epic Profile, Coulter Co.).

**Host Cell Reactivation Assays**—The pMSV-Luc reporter plasmid was damaged in vivo by exposure to 1000 J/m<sup>2</sup> of UV-C light using a Stratagene UV Stratalinker (Stratagene). CREF cells were transfected with 4 μg of UV-irradiated or non-irradiated pMSV-Luc plasmid, together with an undamaged CAT reporter plasmid (pSV2-CAT) and other test plasmids. Forty eight hours after transfection, cells were harvested and resuspended in 400 μl of reporter lysis buffer (Promega). The cell pellet was disrupted by a single freeze-thaw cycle. For the luciferase assay, 25 μl of the total cellular extract was added to 50 μl of luciferase substrate (Promega). Luciferase activity was quantitated in a Turner TD-20e luminometer. CAT assays were performed by a single phase-extraction assay using 25 μl of the total cellular extract as described previously (10). Luciferase activity was normalized to CAT activity of the same extract. Repair activity was calculated by setting normalized luciferase activity from cells cotransfected with non-irradiated pMSV-Luc and test plasmids to 100%. The repair activity of duplicate cells cotransfected with irradiated pMSV-Luc and identical test plasmids was reported as a percentage of that activity.

**Transfection Assays**—HeLa cells were grown in 60-mm dishes and transfected by calcium phosphate precipitation with a total of 14 μg of DNA, which included pSV2-CAT plasmid, pG13pyLuc reporter plasmid, wt p53 or mt p53 expression vectors, and/or pCMV-Tax. Cells were harvested 48 h after transfection and resuspended in 400 μl of reporter lysis buffer. Luciferase and CAT assays were then performed as described above. The luciferase activity was normalized to CAT activity of the same extract. The normalized luciferase activity of cells transfected with the pG13pyLuc alone was set to “1,” and fold activation of the remaining samples was calculated accordingly.

**Statistical Calculations**—Statistical calculations were performed with MINITAB for Windows software (Minitab Inc.). All error bars presented represent the statistical results from more than three independent experiments.

**Results**

**Effect of Tax on PCNA Expression**—We have previously shown that the HTLV-1 Tax protein suppresses cellular NER and that this activity correlates with its ability to activate transcription from the PCNA promoter (8). To determine whether the effect of Tax on the PCNA promoter results in increased endogenous PCNA protein expression in CREF cells, a Tax expression plasmid was transfected into CREF cells, and PCNA protein levels were measured by Western blot (Fig. 1A). The expression of cellular PCNA increased 2.6-fold above basal level (compare lanes 1 and 4) following introduction of 1 μg of Tax expression plasmid. This result correlates well with our previous finding that Tax activates the PCNA promoter. Cells overexpressing PCNA following Tax transfection also showed reduced DNA repair (data not shown) as described previously (8).

PCNA expression in normal cells fluctuates about 2.7-fold throughout the cell cycle with maximal levels being observed in...
Suppression of DNA Repair by HTLV-I Tax

Restoration of Cellular DNA Repair Activity by Wild-type p53—The tumor suppressor p53 is an important regulator of genome stability and is required for efficient repair of DNA damage by NER (37, 38). p53 expression is stimulated in the presence of DNA damage and functions to transcriptionally activate expression of p21 as well as other cellular genes. p21 then binds PCNA to block DNA replication and stimulate DNA repair. The ability of Tax to inhibit p53 function (25, 26) suggests that downstream genes may not be properly regulated in Tax-expressing cells. These effects, in combination with Tax activation of PCNA expression, could coordinately interfere with DNA repair in cells expressing Tax does not result from an indirect effect of Tax on cell cycle progression but rather from activation of the PCNA promoter.

Transactivation Activity of p53 Is Required for Efficient DNA Repair Activity

To examine the effect of p53 overexpression on NER activity suppressed by Tax, DNA repair was measured using a host cell reactivation (HCR) assay (Fig. 2). A reporter plasmid (pMSV-Luc) was UV-irradiated, or mock-treated, and then transfected into CREF cells either with or without p53 and Tax expression plasmids. Since UV-induced lesions provide a strong block to transcription, expression of the UV-irradiated luciferase reporter reflects the repair activity of these cells. As observed previously, Tax alone suppressed NER to about 50% that observed in cells transfected with the backbone vector control, pSV2-neo. This effect was dose-dependent and correlated with induction of PCNA gene expression following Tax transfection into p53-/- cells as previously reported (8). Cotransfection of a wt p53 expression plasmid (p53-LTRA) into CREF cells resulted in a dose-dependent rescue of NER activity suppressed by Tax. The effect of wt p53 on NER was specific since a p53 mutant, p53-LTRV (alanine 146 to valine), which is defective in transactivation activity did not restore DNA repair activity.

Tax Suppresses a p53-dependent Form of DNA Repair—A previous study demonstrated that the rate of point mutation accumulation in wild-type and p53-deficient mouse fibroblasts was indistinguishable (39). This result supports the existence of one or more cellular mechanisms for DNA repair in the absence of p53. Therefore, we wished to confirm that the suppression of DNA repair by Tax involves a p53-dependent pathway. p53-deficient fibroblasts were used to determine whether Tax could interfere with DNA repair in cells that were already lacking p53 (Fig. 3). Consistent with previous studies, the p53-/- fibroblasts retained partial DNA repair activity as compared with p53+/- fibroblasts. Tax expression did not significantly affect repair activity of p53 null cells suggesting that Tax does not interfere with p53-independent DNA repair pathways. Transfection of wild-type p53 or p21 resulted in increased DNA repair activity in the p53 null fibroblasts. However, cotransfection of wild-type p53 together with Tax into p53 null fibroblasts resulted in reduced DNA repair activity similar to the endogenous activity observed in p53 null cells and in cells transfected with Tax alone. These results demonstrate that the suppression of DNA repair by Tax involves a p53-dependent DNA repair pathway.
Repair—p53 has multiple activities including protein interaction and transcriptional activation. Transcriptional activation of downstream cellular genes by p53 is important for maintaining genome stability. The p53 mutant p53-LTRV is a temperature-sensitive mutant that is inactive at 37 °C, but at 32 °C it regains transcriptional activity. To determine whether the transactivation function of p53 contributes to its ability to rescue DNA repair suppressed by Tax, the effect of mt p53 on DNA repair activity was tested in CREF cells at permissive and non-permissive temperatures. At 37 °C, the non-permissive temperature, mutant p53 did not rescue cellular NER suppressed by Tax (Fig. 5, left panel). However, when incubated at 32 °C, the permissive temperature at which mt p53 regains transactivation activity, NER activity suppressed by Tax was restored to levels observed with wt p53 (Fig. 5, right panel).

Cotransfection of a luciferase reporter containing p53 responsive elements (pG13pyLuc) under the same conditions demonstrated that mt p53 was transcriptionally active at 32 °C but not at 37 °C (data not shown). Thus, a p53-dependent gene(s) appears to play a role in the rescue of DNA repair suppressed by Tax.

Restoration of DNA Repair Activity by p21—Since the suppression of DNA repair by Tax appears to involve a p53-dependent pathway, we next investigated whether a downstream target of p53 is involved in suppression of DNA repair by Tax. Following DNA damage, p53 activates transcription of several downstream genes including p21 (15). p21 is an important modulator of NER, facilitating the repair of UV-induced DNA damage (40) by binding to other regulatory proteins. Specifically, p21 binds to PCNA causing a shift in activity of the complex from DNA replication to DNA repair. A C-terminal truncation mutant of p21, which lacks the PCNA-interacting domain, fails to stimulate DNA repair in p21 null cells (41). Thus, p21-dependent DNA repair activity requires PCNA binding and likely involves sequestration of free PCNA. We propose that in the presence of excess PCNA (due to Tax activation) there is insufficient p21 to sequester sufficiently PCNA, and DNA repair cannot proceed. This effect is compounded by the inactivation of p53 function by Tax.

To test this possibility, p21 and Tax expression plasmids were cotransfected into CREF cells. As seen previously, Tax suppressed NER to about 50% that observed in the absence of Tax. The addition of wt p21 (pCMVP21SDI1/HA) resulted in partial rescue of NER activity suppressed by Tax in a dose-dependent manner (Fig. 6). Following transfection of a p21 mutant that lacks the PCNA binding domain (pCMVP21SDI1/HA142–147), DNA repair activity did not differ significantly from that observed in cells expressing Tax alone. The inability of this p21 mutant to restore cellular NER suggests that the rescue of NER by p21 requires its association with PCNA. Analysis of transfected wt and mt p21 by immunoblot showed the expected dose-dependent expression (Fig. 6, bottom). Consistent Tax expression was observed in all cells transfected with the Tax expression vector, and actin expression was monitored to confirm equivalent loading.

**DISCUSSION**

NER is a major cellular defense against the carcinogenic effect of UV irradiation. NER removes UV-induced DNA damage as well as bulky lesions caused by a variety of other genotoxic agents (42). Various types of genetic defects in NER are found in individuals with inherited syndromes that predispose them to cancer such as xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy (for review see Ref. 43). Viral transforming proteins have also been shown to suppress
Thus, overexpression of wt p53 may out-compete CBP binding, resulting in activation of p53-dependent promoters. Alternatively, Tax has been shown to stimulate p53 phosphorylation through an NF-κB dependent mechanism resulting in inhibition of p53 function. The presence of elevated p53 in our study may provide excess substrate for this reaction, resulting in active p53. These possibilities are testable and will be the focus of future studies.

The inhibition of p53 function by Tax appears to contribute to Tax suppression of DNA repair, as overexpression of transcriptionally active p53 rescued repair activity in this study. These results suggest that the inactivation of p53 and subsequently its downstream targets play important roles in Tax suppression of DNA repair. Our demonstration that p21 overexpression restores DNA repair activity suppressed by Tax (Fig. 6) suggests that p21 levels in Tax-expressing cells are insufficient for p21 to regulate DNA repair. We hypothesize that the inactivation of p53 transactivation function in Tax-expressing cells results in reduced p21 expression and, subsequently, free PCNA which can stimulate DNA replication and suppress DNA repair. Thus, the ability of Tax to inhibit p53 function and to activate PCNA expression combine to overcome the normal inhibitory effect of p21 on DNA replication in the presence of DNA damage. Interestingly, Tax has been shown to activate directly expression from the p21 promoter (22). We were unable to confirm Tax transactivation of endogenous p21 levels in CREF cells, so at this time we cannot determine whether direct activation of the p21 promoter plays a role in Tax suppression of NER. However, Tax did not activate a p21 promoter construct driving CAT expression in these cells (data not shown), and transient p21 expression was able to rescue Tax suppression of DNA repair (Fig. 6), suggesting that p21 levels are not significantly elevated in these cells.

Through its effects on p53, p21, and PCNA, Tax interferes with DNA repair and allows cells to replicate in the presence of DNA damage. Reduced DNA repair capacity and replication of damaged DNA promotes fixation of mutations in the genome and increases the chances of cellular transformation, a phenomenon previously known as the mutator phenotype (46). These effects are consistent with the presence of chromosomal abnormalities in HTLV-1-transformed cells and may explain the small percentage of infected individuals who progress to disease and the long period of clinical latency prior to the onset of disease.

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REFERENCES

1. Poiesz, B. J., Ruscetti, F. W., Gadzar, A. F., Bunn, P. A., Minna, J. D., and Gallo, R. C. (1980) Proc. Natl. Acad. Sci. U. S. A. 77, 4715–4719
2. Gessain, A., Barin, F., Vernant, J. C., Gout, O., Maurs, L., Calander, A., and DelThe, G. (1985) Lancet 2, 407–409
3. Kao, S.-Y., Lemoine, J. F., and Marriott, S. J. (2000) Res. Adv. Virol. 1, 1–12
4. Majone, F., Semmes, O. J., and Jeang, K.-T. (1998) Virology 219, 456–459
5. Saggoro, D., Majone, F., Forino, M., Turchetto, L., Lzeal, A., and Chico-Bianchi, L. (1995) Leuk. & Lymphoma 12, 281–286
6. Miyake, H., Suzuki, T., Hirai, H., and Yoshida, M. (1999) Virology 253, 155–161
7. Jeang, K.-T., Widen, S. G., Semmes, O. J., and Wilson, S. H. (1990) Science 247, 1082–1084
8. Kao, S.-Y., and Marriott, S. J. (1999) J. Virol. 73, 4299–4304
9. Phippott, S. M., and Buehring, G. C. (1999) J. Natl. Cancer Inst. 91, 933–942
10. Ressler, S., Morris, G. F., and Marriott, S. J. (1997) J. Virol. 71, 1181–1190
11. Kelman, Z. (1997) Oncogene 14, 629–640
12. Flores-Rozas, H., Kelman, Z., Dean, F. B., Pan, Z.-Q., Harper, J. W., Elledge, S. J., O'Donnell, M., and Hurwitz, J. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 8855–8859
13. Matsumoto, S., Yamaguchi, M., and Matsukage, A. (1994) J. Biol. Chem. 269, 11030–11036
14. Xiong, Y., Zhang, H., and Beach, D. (1992) Cell 71, 505–514
15. El-Deiry, W. S., Tokino, T., Velarde, J. C., Levy, D. B., Parsons, R., Treat,
J. M., Lin, D., Mercer, W. E., Kinzler, K. W., and Vogelstein, B. (1993) Cell 75, 817–825
16. Xiong, Y., Hannon, G. J., Casso, D., Kobayashi, R., and Beach, D. (1995) Nature 371, 534–537
17. Luo, Y., Hurwitz, J., and Massague, J. (1995) Nature 375, 159–161
18. Mozzherin, D. J., McConnell, M., Jasko, M. V., Krayevsky, A. A., Tan, C. K., Downey, K. M., and Fisher, P. A. (1996) J. Biol. Chem. 271, 31711–31717
19. Mozzherin, D. J., Shibutani, S., Tan, C. K., Downey, K. M., and Fisher, P. A. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 6126–6131
20. Donehower, L. A., and Bradley, A. (1993) Cell 75, 817–825
21. Donehower, L. A., and Bradley, A. (1993) Biochim. Biophys. Acta 1155, 181–205
22. Cereseto, A., Diella, F., Mulloy, J. C., Cara, A., Michieli, P., Grassmann, R., Franchini, G., and Klotman, M. E. (1996) Blood 88, 1551–1560
23. Uittenbogaard, M. N., Giebler, H. A., Reisman, D., and Nyborg, J. K. (1995) J. Biol. Chem. 270, 28503–28506
24. Akagi, T., Ono, H., Tsuchida, N., and Shimotohno, K. (1997) FEBS Lett. 406, 263–266
25. Mulloy, J. C., Kislyakova, T., Cereseto, A., Casareto, L., LoMonico, A., Fullen, J., Lorenzi, M. V., Cara, A., Nicot, C., Giam, C. Z., and Franchini, G. (1998) J. Virol. 72, 8852–8860
26. Pise-Masison, C. A., Chui, K. S., Radonovich, M., Dittmer, D., Kim, S. J., and Brady, J. N. (1998) J. Virol. 72, 6348–6355
27. Ariumi, Y., Kaida, A., Lin, J. Y., Hirota, M., Masui, O., Yamaoka, S., Taya, Y., Shimotohno, K. (2000) Oncogene 19, 1491–1499
28. Reid, R. L., Lindholm, P. F., Mireskandari, A., Dittmer, D., and Brady, J. N. (1993) Oncogene 8, 3029–3036
29. Gartenhaus, R. B., and Wang, P. (1995) Leukemia (Baltimore) 9, 2082–2086
30. Kao, S. Y., Lemoine, F. J., and Marriott, S. J. (2000) Oncogene 19, 2240–2248
31. Nakanishi, M., Robetorye, R. S., Pereira-Smith, O. M., and Smith, J. R. (1995) J. Biol. Chem. 270, 17060–17063
32. Gartenhaus, R. B., and Wang, P. (1995) Leukemia (Baltimore) 9, 2082–2086
33. Lydy, S. L., Conner, M. E., and Marriott, S. J. (1998) Virology 250, 60–66
34. Sheiky, M. S., Smith, Y. Q., O’Connor, P. M., and Fornace, A. J., Jr. (1995) Oncogene 10, 1053–1095
35. Sands, A. T., Suraokar, M. B., Sanchez, A., Marsh, J. E., Donehower, L. A., and Bradley, A. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 8517–8521
36. Sheiky, M. S., Smith, Y. Q., O’Connor, P. M., and Fornace, A. J., Jr. (1995) Oncogene 10, 1053–1095
37. Ford, J. M., and Hanawalt, P. C. (1997) J. Biol. Chem. 272, 28073–28080
38. Smith, M. L., Chen, I.-T., Zhan, Q., O’Connor, P. M., and Fornace, A. J., Jr. (1997) Oncogene 14, 1875–1882
39. McDonald, E. C., Walker, G. C., and Siede, W. (1995) DNA Repair and Mutagenesis, pp. 283–288, American Society for Microbiology, Washington, D. C.
40. Becker, S. A., Lee, T. H., Butel, J. S., and Slagle, B. L. (1998) J. Virol. 72, 2250–2255
41. Ford, J. M., Baron, E. L., and Hanawalt, P. C. (1996) Cancer Res. 56, 2250–2255
42. Friedberg, E. C., Walker, G. C., and Siede, W. (1995) DNA Repair and Mutagenesis, pp. 283–288, American Society for Microbiology, Washington, D. C.
43. Wood, R. D. (1996) Annu. Rev. Biochem. 65, 135–167
44. Becker, S. A., Lee, T. H., Butel, J. S., and Slagle, B. L. (1998) J. Virol. 72, 266–272
45. Ford, J. M., Baron, E. L., and Hanawalt, P. C. (1996) Cancer Res. 56, 599–603
46. Loeb, L. A. (1991) Cancer Res. 51, 3075–3079