Numerous studies have revealed that a part of the cellular mechanism to combat oxidative stress involves increased antioxidant capacity. However, another defense mechanism that has received less attention is DNA repair. Because of the important homeostatic role of mitochondria and the exquisite sensitivity of mitochondrial DNA (mtDNA) to oxidative damage, we hypothesized that mtDNA repair plays an important role in the protection against oxidative stress. To test this hypothesis, mtDNA damage and repair was evaluated in normal HA1 Chinese hamster fibroblasts and oxidative stress-resistant variants isolated following chronic exposure to H2O2 or 95% O2. Reactive oxygen species were generated enzymatically using xanthine oxidase and hypoxanthine. When treated with xanthine oxidase reduced levels of initial mtDNA damage and enhanced mtDNA repair were observed in the cells from the oxidative stress-resistant variants, relative to the parental cell line. This enhanced mtDNA repair correlated with an increase in mitochondrial apurinic/apyrimidinic endonuclease activity in both H2O2- and O2-resistant HA1 variants. This is the first report showing enhanced mtDNA repair in the cellular response to chronic oxidative stress. These results provide further evidence for the crucial role that mtDNA repair pathways play in protecting cells against the deleterious effects of reactive oxygen species.

Oxidative stress occurs in cells when the equilibrium between prooxidant and species favors prooxidant stress. It is due to reactive oxygen species (ROS) generated by exogenous factors or by cellular metabolism. ROS can interact with multiple different macromolecules including lipids, nucleic acids, and proteins. As a result, cells have evolved numerous defense systems to counteract the deleterious effects of agents. A variety of cellular antioxidants have been identified that specifically eliminate ROS. These include superoxide dismutases, catalases, glutathione, α-tocopherol, vitamins A and C, and melatonin. However, antioxidants are not able to fully protect DNA from oxidative stress, and various lesions in DNA such as base modifications, degradation products of deoxyribose, and strand breaks are known to occur. Therefore, the second line of defense against oxidative stress involves DNA repair.

Within mammalian cells, there are two distinct genomes; one is located in the nucleus, and the other in mitochondria. Although damage and repair of nuclear DNA has been a subject of intense study for many years, more recently interest in mtDNA damage and repair has come to the forefront with the discovery that defects in the mitochondrial genome are associated with many pathologies and that there are a number of chemotherapeutic agents that work through the initiation of mtDNA damage (1, 2). In addition, it is well established that mitochondria play a variety of essential roles in cellular metabolism, including the production of ATP through oxidative phosphorylation, regulation of calcium homeostasis in cell signaling pathways, and initiation of apoptotic signal cascades (3, 4).

Because we and others have found that mtDNA is a sensitive target for oxidative damage (5–7), the objective of the present study was to investigate the role that mtDNA damage and repair plays in the cellular response to chronic oxidative stress. For these studies, we used cell lines isolated from HA1 Chinese hamster fibroblasts that became resistant to oxidative stress following chronic exposure to progressively increasing concentrations of H2O2 (OC14 cells) or to high concentrations of molecular oxygen (O2R95 cells) (8–11). These lines are cross-resistant to other oxidative stresses, including oxygen toxicity (10, 11). Furthermore, H2O2- and O2-resistant variants of HA1 cells have an increased ability to metabolize toxic oxidants including hydrogen peroxide and lipid peroxidation-derived aldehydes (8–10). This increased resistance to toxic oxidants is accompanied by pronounced increases in several cellular antioxidant defenses, including copper-zinc superoxide dismutase, catalase, total glutathione, glutathione peroxidase activity, and glutathione transferase activity (8–11).

mtDNA damage and repair was evaluated following exposure to ROS. Both resistant variants displayed reduced levels of initial mtDNA damage and a greater capacity to repair oxidative lesions in this DNA. To elucidate some of the mechanisms involved in this enhanced mtDNA repair in the resistant cell lines, we investigated the activities of several major DNA repair enzymes involved in mitochondrial base excision repair enzymes (BER) using abasic site (AP)-, 8-oxoguanine (8-OxoG)-, and thymine glycol (Tg)-containing oligonucleotides as substrates. The results showed that mitochondrial APE activity was significantly augmented in both the H2O2- and O2-resistant HA1 variants. No significant changes were found in removal of either 8-OxoG or Tg between oxidative stress-resistant variants and parental HA1 cells. As expected, both
oxidative stress-resistant variants showed more efficient survival following treatment with XO compared with the parental
HA1 line. These results, to our knowledge, are the first to document enhanced mtDNA repair in the cellular response of
cells to chronic oxidative stress.

EXPERIMENTAL PROCEDURES

Cell Culture—Chinese hamster fibroblasts designated HA1 and their stable
H2O2-resistant (OC14) and O2-resistant (O1R5) variants were
maintained in Kagle’s minimal essential medium supplemented with
10% fetal calf serum (HyClone, Logan, UT) and 0.05 mg/ml gentamicin.
Cultures were grown at 37 °C in a humidified incubator with a mixture of
5% CO2 and air. For the repair studies, ~1.5 × 10^7 cells were plated
per 150-mm dish. The cultures were used for experiments ~3 days after
plating.

Drug Preparation and Exposure—HA1 cells and their resistant vari-
ants were exposed to different concentrations of XO (Grade III from
buttermilk; Sigma) ranging from 5 to 600 milliunits/ml. A constant
concentration of 0.5 mM hypoxanthine (Sigma) was used. Initially,
hypoxanthine was dissolved in Hanks’ balanced salt solution (HBSS),
and different amounts of XO were subsequently added to the medium.
The cells were rinsed with HBSS and then exposed to XO for 15 min
in a 150-mm dish. The cultures were plated in HBSS under the same conditions. After 15 min, the cells were lysed for
dose–response experiments or rinsed and placed in culture medium
with time to allow for repair.

Mitochondrial DNA Damage and Repair Assay—Following drug ex-
posure or after different times for repair, the cells were lysed in 10 mM
Tris, 1 mM EDTA (pH 8.0), 0.5% SDS, and 0.3 mg/ml proteinase K and
incubated overnight at 37 °C, and precipitated again with cold ethanol.
DNA was extracted, precipitated with 2.5 M ammonium acetate and 2 volumes of
cold ethanol, resuspended in water, treated with DNase-free RNase (~1
mg/ml) for 2 h at 37 °C, and precipitated again with cold ethanol.

Purified DNA was digested overnight with KpnI (10 units/μg DNA), precipitated,
resuspended in TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), and quantified using Hoechst 33258 dye and a Hoeffer TFK 100
Fluorometer (Hoefer Scientific Instruments, San Francisco, CA). Samples containing 5 μg of DNA were
heated at 70 °C for 15 min and then cooled at room temperature for 20
min. A sodium hydroxide solution then was added to a final concentra-
tion of 0.1 N, and samples were incubated for 15 min at 37 °C. This
alkali treatment produced single strand breaks at all abasic or sugar-
modified sites in the DNA. Gel electrophoresis and vacuum transfer
were carried out as described previously (12). Following a prehybrid-
ization, the membranes were hybridized with a denatured PCR-gener-
ated mitochondrial probe (5), washed according to the manufacturer,
placed under phosphorus imaging screens, and scanned for detection of
hybridization bands. The resulting band images were scanned using a Bio-Rad GS-250 molecular imager. Break frequency was determined
by using the Poisson expression (16), which is given by:

\[
P(t) = e^{-\lambda t}
\]

where \(P(t)\) is the percentage of breaks per fragment, and \(P_f\) is the fraction of fragments free of breaks.

The percentage of repair at time \(t\) was calculated by subtracting the
breaks at time \(t\) from the breaks present at 0 h and dividing by the
breaks present at 0 h. The resulting value then was converted to a percentage
by multiplying by 100.

Preparation of Mitochondrial Fractions—Mitochondrial protein frac-
tions were isolated from one 150-mm dish of each cell type (HA1 cells
and their resistant variants). The cells were harvested and treated with
ice-cold digitonin (325 mM digitonin, 2.5 mM EDTA, 250 mM mannitol,
and 17 mM MOPS, pH 7.4) for 80 s. The lysed cells were then added to
mannitol-acetone buffer to a final strength of 1 (210 mM mannitol, 70
mM sucrose, 50 mM EDTA, 5 mM Tris, pH 7.5). The suspension was
centrifuged 10 min at 800 × g at 4 °C to pellet nuclei. The super-
natant was centrifuged once more at 10 min at 800 × g at 4 °C to
remove nuclear debris. The mitochondrial fraction was pelleted by
centrifugation at 20,000 × g at 4 °C for 20 min. Isolated mitochondria
were suspended in a buffer of 10 mM HEPES, pH 6.5, 100 mM KCl, 10
mM MgCl2, 5 mM dithiothreitol, 5% glycerol, and 5 μl of protease
inhibitors mixture/ml (Sigma). These suspensions were briefly soni-
cated and centrifuged once more at 10,000 × g to pellet any
remaining debris. Supernatant proteins from mitochondrial enriched
fractions were used for APE activity assays. The purity of these frac-
tions was routinely evaluated by Western blot analysis as has been
documented in our previous publication (13). For the assays to detect
8-OxoG and Tg removal, mitochondria were suspended in a buffer of 20
mM HEPES, pH 7.4, 1 mM EDTA, 5 mM dithiothreitol, 100 mM KCl, 5% glycerol, and 5 μl of protease inhibitors mixture/ml. The protein con-
centration was determined using the Bio-Rad protein dye microassay
according to the manufacturer’s recommendation (Bio-Rad).

APE Activity Assays—A 21-mer oligonucleotide with a tetrahidrofu-
rurate adduct (THF-AP) at the 5′ position (Trevigen, MD) was
end-labeled. The labeling reaction contained 20 pmol of single-
stranded THF-AP oligonucleotide, 5 pmol of [γ-^32P]ATP, T4 polynucleo-
tide kinase (Promega, Madison, WI), and appropriate kinase buffer in
a total volume of 20 μl (incubation for 45 min at 37 °C followed by 10 min
at 68 °C). Complementary oligonucleotide (20 pmol) then was added at
room temperature to form duplex DNA. Equal amounts of mitochon-
drial extracts (50–100 μg) were used in assays with the labeled duplex
oligonucleotide. Activity assays contained 1 pmol of labeled duplex
oligonucleotide, 2 μl of 10× REC buffer (10 mM HEPES, pH 6.5, 100 μM
KCl, 10 mM MgCl2) and organellar extracts or 2.5 μl of control APE
enzyme (Trevigen) in a total volume of 20 μl. The reaction mixtures
were incubated for various times at 37 °C. Formamidobromphenol (80%:
0.2%) dye was added to the mix to stop the reaction, and the
reaction products were analyzed by electrophoresis in 20% polyacrylamide, 8 M urea gels. Wet gels were autoradiographed at ~70 °C. Autoradiographs were scanned using a Bio-Rad GS-250 molecular imager, and the densitometry values were analyzed by using Molecular Analyst (Bio-Rad) software.

Removal of 8-OxoG and Tg—8-OxoG- and Tg-containing DNA du-
plexes were prepared, and specific reaction assays were performed as
described previously (12–14). Equal amounts of proteins (10–15 μg)
from mitochondrial fractions isolated from resistant HA1 variants and
the parental cell line were used. In the control reactions, 5 units of
either pure formamidopyrimidine DNA glycosylase enzyme (Trevigen)
or endonuclease III (Trevigen) was added instead of cell lysates.

The reaction mixtures in a total volume of 20 μl were incubated for ~3–20 h
at 37 °C. Following polyacrylamide gel electrophoresis, the resultant
incisions were analyzed by using Molecular Analyst software.

Cell Viability and Survival Experiments—For viability studies, HA1
cells and their resistant variants were plated into 24-well plates and
exposed to the concentrations of xanthine oxidase that were used for
subsequent repair studies (HA1, 50 milliunits; OC14, 600 milliunits;
O1R5, 300 milliunits). Following a 15-min exposure to XO, the cells
were rinsed with HBSS, and complete medium was replaced for 2 or
more times, and the cells were then exposed to the concentrations of
the drug diluted in complete medium. 8-OxoG- and Tg-containing cells
were counted using light microscope. The percentage of viable cells was plotted as a function of time. For survival experiments,
evolutionarily growing cultures with 2.5–2.8 × 10^6 cells/60-mm plate
were rinsed once with HBSS, and 4 ml of fresh HBSS containing 0.5 mM
hypoxanthine was added to each dish. The reaction was then initialized
by the addition of the indicated amount of XO, and the treatment
continued for another 15 min. Control wells were treated with the
drug diluent only. Following treatment, each cell culture was washed with sterile
Puck saline folowed by removal using trypsin. The resulting single
cell suspension was counted (Coulter counter), diluted, and plated for
clonogenic cell survival. After ~8–10 days of incubation at 37 °C, the
colonies were fixed (70% ethanol), stained with Coomassie Blue, and
counted using a dissecting microscope. The dilution replicates, which
yielded 50–250 surviving colonies, were used for survival analysis. A
colon was considered a survivor. Plating efficiencies were 60–90% for all untreated cell lines. Surviving fractions
were normalized to the appropriate untreated control and plotted ver-
sus the dose of cytotoxic agent.

Statistical Analysis—The data are presented as the means ± S.E. of
three independent experiments. The data were compared using a standard
t test, and statistical significance was determined at the 0.01 level.

RESULTS

Cell Viability Studies—To ensure that the XO doses used for the repair experiments were not toxic to the analyzed cells,
metabolic viability studies using the trypan blue excision method were performed. The cells were treated with different
concentrations of XO, as described under “Experimental
Procedures,” and cell viability was determined immediately after
treatment (0 h) and 2 and 24 h later. As can be seen in Table I,80% or more of the cells in each cell line were viable after

treatment with XO.

Clonogenic Survival—Following XO exposure, the cells were
trypsinized and replated at equivalent densities (1000 cells/ plate). After ~8–10 days, the colonies were fixed and stained
with Coomassie Blue, and colonies containing 50 or more cells
ROS-resistant variants showed enhanced survival following XO exposure. Exponentially growing cultures with 2.5–2.8 × 10^6 cells/60-mm plate were treated with the indicated amount of XO as described under “Experimental Procedures.” Following treatment, each cell culture was washed with sterile Pucks saline followed by removal using trypsin. The resulting single cell suspension was counted, diluted (1000 cells/60-mm plate), and plated for clonogenic cell survival. After 8–10 days, the colonies were fixed, stained with Coomassie Blue, and counted using a dissecting microscope. Dilution replicates then were incubated with labeled THF-AP substrate. As a positive control, human APE (Trevigen) was used. As illustrated in Fig. 5 APE activity was significantly increased in both the O_2^- and H_2O_2-resistant variants repair oxidative damage more rapidly then the parental HA1 line (Fig. 4).

**Activation of Mitochondrial APE by ROS**—Having determined that stable oxidative stress-resistant derivations from HA1 cells demonstrated a greater capacity for mtDNA repair, we evaluated whether the up-regulation of mitochondrial APE activity could contribute to the increase of mtDNA repair in these resistant variants. Mitochondrial protein extracts were isolated from HA1 cells and their resistant variants. The extracts then were incubated with labeled THF-AP substrate. As a positive control, human APE (Trevigen) was used. As illustrated in Fig. 5 APE activity was significantly increased in both resistant variants compared with the parental cell line.

**Removal of 8-OxoG and Tg in Parental HA1 Cells and Oxidative Stress-resistant Variants**—To determine the effect of chronic oxidative stress on removal of 8-OxoG and Tg, mitochondrial protein extracts were isolated from HA1 cells and...
their resistant variants. Reaction mixtures in a total volume of 20 μl were incubated for 3–20 h at 37 °C. The data in Fig. 6 show that there were no significant differences in the removal of either adduct between parental HA1 and oxidative stress-resistant variants.

**Fig. 3.** Higher concentrations of XO were necessary to generate equivalent mtDNA damage in H2O2- and O2-resistant variants when compared with the parental HA1 cells. To optimize levels of damage for the repair experiments, XO doses were increased for the resistant variants. The HA1 parental cell line was exposed to 50, 25, and 5 milliunits/ml of XO and 0.5 mM hypoxanthine. OC14 cell were treated with 600, 300, and 150 milliunits/ml of XO, whereas O2R95 cells were exposed to 300, 150, and 50 milliunits/ml of XO. A, a representative autoradiogram of a Southern blot analysis of mtDNA damage from each cell type. B displays the quantitation of strand brakes in mtDNA from these experiments. The data are expressed as the means of three separate experiments ± S.E. C, control.

**Fig. 4.** Resistant cells revealed a greater capacity for mtDNA repair. A, representative autoradiographs of quantitative Southern blots for each cell type are displayed. B, the percentage of repair for all three cell lines are displayed. Note that higher concentrations of XO were used for both resistant variants. The data are the means ± S.E. of three separate experiments. An asterisk indicates a significant difference (p < 0.01). C, control.

**Fig. 5.** Increased APE activity in ROS-resistant variants. Mitochondrial extracts were isolated from HA1 cells and their resistant variants as described under “Experimental Procedures.” Equal amounts of mitochondrial protein extracts were incubated with labeled THF-AP substrate for a various times. The data are the means ± S.E. of three separate experiments. An asterisk indicates a significant difference (p < 0.01).

**Fig. 6.** Specific activities for removal of 8-OxoG and Tg in parental and chronic oxidative stress-resistant cells are similar. A, 8-OxoG removal in HA1 cells and chronic oxidative stress-resistant cells. The values are the means ± S.E. of three separate experiments. B, Tg removal in HA1 parental cells and chronic oxidative stress-resistant variants. The values are the means ± S.E. of three separate experiments.

**DISCUSSION**

There are three novel observations in this study. First, it has been shown that cells resistant to oxidative stress have a reduced level of initial mtDNA damage. Second, mtDNA repair is involved in the cellular response to chronic oxidative stress. Third, increased mtDNA repair correlates with enhanced mitochondrial APE activity. In the present study we used HA1 hamster fibroblasts and their stable oxidative stress-resistant variants, which were derived following chronic exposure to H2O2 or 95% O2. In the first set of experiments, we investigated the formation of mtDNA damage in response to ROS generation. Our data reveal that OC14 and O2R95 cells are quite resistant to ROS generated by XO. This finding can partially be explained by the high levels of antioxidants induced following chronic oxidative stress (8–11). To overcome this resistance and induce the same level of mtDNA damage in all three types of cultures analyzed, increased doses of XO for the resistant variants were required (12-fold for OC14 cells and 6-fold for O2R95 cells). The results of these studies revealed that the...
removal of oxidative lesions was dramatically more efficient in the oxidative stress-resistant variants compared with the parental line. To evaluate the effects of exposure to chronic oxidative stress on mtDNA repair.

Most, if not all, ROS-induced oxidative lesions in DNA are repaired via a BER pathway (15, 16). Previously it has been shown that expression of BER enzymes could be activated in cells by both alkylating (17) and oxidizing agents (18–21). APE is a major enzyme involved in BER both in the nucleus and mitochondria, and so far, it is one of the best characterized of the enzymes involved in BER in the mammalian response to genotoxic stress. Many reports (reviewed in Ref. 22) have provided convincing evidence that the expression of the APE1 gene is inducible by oxidative stress and that overexpression of the APE1 protein in the nucleus helps protect cells against the genotoxic and cell killing effects of ROS, whereas down-regulation of this repair enzyme sensitizes cells to these effects. Little is known about the mechanisms of induction of BER in mitochondria. It has been reported that APE translocates into mitochondria in response to oxidative stress, and therefore, it was speculated that it could participate in the protection of mtDNA against oxidative damage (23). Our data show that mitochondrial APE activity is increased in the stable resistant variants derived from HA1 cells, and this increased activity correlates well with their better ability to repair mtDNA damage following oxidative stress. We believe that increased APE activity in mitochondria could be the result of either increased expression of APE in the mitochondria of resistant variants or increased turnover of this enzyme in mitochondria of ROS-resistant variants. To make a distinction between these two possibilities, further studies need to be performed. A recent study using ρ0 cells, which are deficient in mitochondrial respiration and have reduced levels of endogenous ROS, has shown that these cells also have lower cellular, nuclear, and mitochondrial levels of APE1 (24). When oxidative stress was introduced to ρ0 cells, APE1 levels and APE1 activity increased rapidly to wild type levels. This finding indicates that ρ0 cells retain the ability to modulate APE1 in response to oxidative stress. These data suggest that ROS-induced regulation of mitochondrial APE1 is a general feature of mitochondrial BER in human cells (24), and our data showing increased APE1 activity in the oxidative stress-resistant variants support this notion. Because our results showed that mitochondrial APE1 activity was increased in both H2O2- and O2-resistant variants, and this resistance correlates with their enhanced ability to repair mtDNA damage following oxidative stress, it is tempting to speculate that mitochondrial APE1 is an important part of the cellular response mechanism activated by genotoxic oxidative stress. However, to fully elucidate the role of APE1 in the resistance to chronic oxidative stress, future studies utilizing expression inhibitors are required.

Although we tested mitochondrial extracts from HA1 and its resistant variants for activity to remove 8-OxoG or TG, we were unable to find any differences in the induction of these repair enzymes between the three cell lines. There are mixed reports concerning the role of oxidative stress in influencing other BER enzymes, such as 8-oxoguanine DNA glycosylase/apurinic lyase expression. Some reports have suggested that the induction of human 8-oxoguanine DNA glycosylase/apurinic lyase expression is associated with oxidative stress (25–27), whereas other studies have failed to observe such an effect (28, 29). In agreement with our findings, a recent report showed that human 8-oxoguanine DNA glycosylase/apurinic lyase expression is induced by a DNA-alkylating agent but not by the ROS producing agent H2O2 in human colorectal carcinoma cells (30). Improved mtDNA repair in chronic oxidative stress adopted cell lines correlated with increased cell viability following XO exposure, as evaluated by a clonogenic assay. Although the involvement of mtDNA repair in enhanced survival of cells after exposure to chronic oxidative stress needs to be investigated more thoroughly, recent data from our laboratory greatly support this idea. In a number of studies, we have demonstrated that overexpression of DNA repair enzymes in mitochondria leads to increased mtDNA repair damage and increased cellular survival (12–14, 31, 32).

In summary, our results show that in addition to the ability to detoxify ROS through the expression of the antioxidant enzymes, enhanced mtDNA repair capacity, because of the increased activity of specific mitochondrial BER enzymes, may contribute to cellular resistance to oxidative stress and thus initiate drug resistance. Altering of the mtDNA repair capacity perhaps through the inhibition of mitochondrial APE1 expression represents a potentially novel strategy to overcome the acquired drug resistance in neoplastic cells to genotoxic agents that presently plague the use of cancer chemotherapeutic agents.

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