Human Ogg1, a Protein Involved in the Repair of 8-Oxoguanine, Is Inhibited by Nitric Oxide

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ABSTRACT

NO-mediated inhibition of base excision DNA repair may potentiate oxidative DNA damage in cells and could be relevant to carcinogenesis associated with chronic inflammation. Because 8-oxoguanine, a ubiquitous oxidative DNA lesion, is repaired primarily by human 8-oxoguanine glycosylase (hOgg1), our aim was to determine whether NO directly inhibits its repair activity. Neither induction of NO-generating enzyme inducible NO synthase nor treatment with S-nitroso-N-acetyl-d-1-penicillamine altered expression of hOgg1 in a human cholangiocarcinoma cell line (KMBC). In contrast, both treatments completely inhibited activity of hOgg1 immunoprecipitated from KMBC cells overexpressing hOgg1 and in a cell-free system. Both NO and peroxynitrite were capable of inhibiting hOgg1 activity. Inhibition of hOgg1 protein was characterized by formation of S-nitrosothiol adducts and loss/ejection of zinc ions. Our data indicate that NO, an inflammatory mediator, directly inhibits a key base excision repair enzyme (hOgg1) responsible for base excision repair of 8-oxoguanine. These data support the concept that NO-mediated inhibition of DNA contributes to the mutagenic environment of chronic inflammation.

INTRODUCTION

Chronic inflammation of gastrointestinal mucosa predisposes individuals to the development of carcinoma in the affected tissues. For example, chronic inflammation of the esophagus, gastric mucosa, pancreas, colon, and liver is a well-established risk factor for malignant transformation in these organs (1–3). Although the cellular mechanisms culminating in malignant transformation of epithelial cells are complex and multifactorial, there is increasing evidence implicating NO as a link between inflammation and carcinogenesis (4). First, chronic inflammation is associated with induction of iNOS,3 and this enzyme efficiently generates NO (5). Second, NO has been suggested to promote cancer development by acting as an endogenous mutagen, an angiogenesis factor, a mitogen, an enhancer of proto-oncogene expression (6), and an inhibitor of apoptosis (7, 8). Finally, many advanced cancers continue to express iNOS, which suggests that NO contributes to tumor progression (9, 10). Collectively, these data are consistent with a key role for NO in the initiation, promotion, and progression of many human gastrointestinal cancers.

We have been interested in how NO functions as a mutagen using biliary epithelial cells (cholangiocytes) and cholangiocarcinoma cell lines as model systems (11, 12). Our studies have demonstrated that iNOS is not expressed in normal cholangiocytes but is expressed in cholangiocarcinomas of patients with chronic biliary tract inflammation such as primary sclerosing cholangitis, a disease known to predispose individuals to the development of cholangiocarcinoma (11). The expression of iNOS in cholangiocytes is also associated with accumulation of 8-oxoG lesions; 8-oxoG is a dominant oxidative DNA lesion that is highly mutagenic because it predisposes to the development of GC→TA transversions (13, 14). Because 8-oxoG is efficiently repaired in humans by the BER pathway (15, 16), the accumulation of this oxidative DNA lesion in iNOS-expressing cholangiocytes suggests an inhibition of DNA repair. Indeed, we have shown inhibition of both global and base excision DNA repair in cholangiocytes and cholangiocarcinoma cell lines by a NO-dependent repair mechanism (12). The inhibition of DNA repair by NO could be blocked by NO scavengers but not by inhibitors of the NO-mediated, cGMP-dependent signal transduction pathway (12). These observations suggest that NO may directly inhibit DNA repair enzymes including those responsible for BER. Given the importance of the BER pathway in preventing mutagenesis after oxidative DNA damage, more information is needed with regard to how NO disrupts this pivotal antimitagenees safeguard.

Oxidative DNA damage is predominantly repaired by BER enzymes. The predominant oxidative mutagenic lesion 8-oxoG in humans is removed by a BER glycosylase termed Ogg1 that is ubiquitously expressed and maps to chromosome 3p26.2 (15, 16). Studies from mice deficient in the gene for murine Ogg1 demonstrate that this enzyme is responsible for >95% of BER activity in mammalian cells (17). Two isoforms of Ogg1 are expressed due to alternative splicing of a single mRNA gene product. The Ogg1-1a protein is localized to the nucleus, and the Ogg1-2a is localized to the mitochondria (18). Ogg1 contains critical thiol moieties that are necessary for catalytic activity (19). The Ogg1 protein has two distinct DNA-binding motifs, a helix-hairpin-helix motif and a C3H2 zinc finger motif (15). Like other zinc finger proteins (20), Ogg1 is potentially susceptible to nitrosylation of its thiol moieties (21, 22). Thiol nitrosylation can disrupt the zinc finger motif, resulting in loss of the zinc ion and irreversible disruption of catalytic activity (23).

Thus, the objective of the current study was to determine whether hOgg1-1a is a direct target for nitrosylation with resultant loss of catalytic activity. We used a cholangiocarcinoma cell line for these studies as a model system because the biliary epithelium is a target of chronic inflammation in a variety of cholangiopathies that predispose individuals to the development of cancer. We demonstrate that cellular hOgg1-1a-mediated BER activity is inhibited during exposure to NO. This inhibition was associated with protein nitrosylation and ejection of zinc. These data suggest that NO generated during human inflammatory diseases not only causes oxidative DNA damage but also prevents DNA repair by directly inhibiting key DNA repair enzymes. The inability to repair oxidative DNA lesions would be predicted to be mutagenic and increase the risk of carcinogenesis.
MATERIALS AND METHODS

Cell Culture. KMBC, a cell line derived from a human cholangiocarcinoma, was used for these studies (24). The cells were cultured in DMEM (Life Technologies, Inc., Gaithersburg, MD) supplemented with 2 mM l-glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, and 5% fetal bovine serum and maintained at 37°C with 5% CO2 and 95% humidity.

Transfection of KMBC Cells with hOgg1-1a. The corresponding cDNA for human Ogg1 protein was engineered into mammalian expression plasmid pcDEBΔ-Ogg1-1a (25). The plasmid was constructed by inserting the corresponding cDNA fragment, to which a sequence for the HA epitope was introduced (25). Transfection of the KMBC cells was carried out using a 4:1 (w/w) ratio of LipofectAMINE Plus (Life Technologies, Inc.):plasmid DNA. The lipid-DNA complexes were overlaid on 70% confluent KMBC cells and incubated at 37°C with 5% CO2 and 95% humidity in serum-free media for 24 h. After transfection, the cells were incubated for an additional 24 h with complete growth media. The transfection efficiency was determined by transfecting cells with pEGFP-C1 (Clontech, Palo Alto, CA) and assessing the percentage of GFP-expressing cells by fluorescence microscopy; the transfection efficiency was approximately 60%. The transfected cells were incubated in the presence of a mixture of inflammatory cytokines (0.5 ng/ml rhIL-1β, 500 units/ml rhTNFα, and 100 units/ml rhIFNγ) to bind specifically to the HA-tagged protein and subsequently incubated with 0.2% Triton X-100 and incubated with a 1:100 dilution of C. The cells were permeabilized in 0.2% Triton X-100 and incubated with a 1:100 dilution of rabbit anti-HA (Santa Cruz Biotechnology, Santa Cruz, CA) primary antibody to bind specifically to the HA-tagged protein and subsequently incubated with a goat anti-rabbit Texas Red-tagged secondary antibody (1:400 dilution). The cells were mounted and visualized on a fluorescence microscope.

Western Blot Analysis. Cells were harvested by trypsinization and lysed in ice-cold lysis buffer containing 100 mM Tris-HCl (pH 7.5), 0.5 mM EDTA, 0.5 mM EGTA, 2 mM DTT protease inhibitors (5 mg/ml leupeptin, pepstatin, and chymostatin and 87 mg/ml phenylmethylsulfonyl fluoride), and 1% Triton X-100 for 20 min. Whole cell lysates were boiled in Laemmli buffer and incubated at 85°C for 20 min. The methyl methanethiosulfonate was then removed by agitated with rolling action at 4°C for 2 h. The NO scavenger, 100 μM C-PTIO, the peroxynitrite scavenger, 40 μM MnTBAP, and the iNOS inhibitor, 50 μM 1400W, were added to the enzyme buffer.

Specific DNA Repair Assay. hOgg1-1a activity was assayed by determining the ability of WCEs and immunoprecipitated hOgg1-1a protein to recognize and excise 8-oxodG. A 24-base DNA oligonucleotide, 5’-GAAGATTGTGGAATCCCCGGCCTGCG-3’ (Trevigen, Gaithersburg, MD), containing an 8-oxodG oxidative lesion at position 10 from the 5’ end and its complement were used as substrates. The calculated ratio of enzyme:substrate was ~2.5:1. A total of 50 pmol of the 24-nt oligonucleotide substrate with the 8-oxodG lesion was radiolabeled with 4 mM [α-32P]ATP (6000 Ci/mmol, New England Nuclear Life Sciences Products, Boston, MA) using poly nucleotide kinase and incubated for 45 min at 37°C. The specific repair activity was assayed by incubating 0.5 pmol of radiolabeled oligonucleotide with 1.5 pmol of its complement in 10 mM Tris (pH 7.5), 1 mM EDTA, and 50 mM NaCl at 37°C for 2 h. Positive control experiments with bacterial 8-oxodG repair enzyme, formamidopyrimidine glycosylase, were run simultaneously. The reaction was loaded onto a 15% acrylamide/7.5 urea/1× Tris-borate EDTA gel. The gel was gel blotted with 3% polyvinylidene difluoride (Millipore, Bedford, MA) for 4 min. Autoradiograms were analyzed using ImageQuant software (Molecular Dynamics).

Assay for Protein S-Nitrosylation. S-Nitrosylation of hOgg1 was assessed using both an immunochemical assay and a biochemical assay. An immunochemical assay (28) was used to detect the formation of S-nitrosylated hOgg1-1a protein. HA-tagged hOgg1-1a protein was immunoprecipitated from control cells and cells treated with SNAP, cytokine mixture, and cytokine mixture plus 1400W. The purified protein was first treated with 20 mM methyl methionine sulfoxonate (Pierce, Rockford, IL) for 1 min at room temperature. Next, 25% SDS was added to block free thiols, and the mixture was incubated at 50°C for 20 min. The methyl methionine sulfoxonate was then removed by desalting three times with the microBioSpin6 (Clontech) column. The nitrosothiol bonds in the hOgg1 protein were selectively reduced with 1 mm sodium ascorbate to thiols. The thiols were reacted at 25°C for 1 h with 4 mM Biotin-HPPD (Pierce), a sulfydryl-specific biotinylating reagent (29). Because the cysteine biotinylation in this assay is reversible, SDS-PAGE sample buffer was prepared without reducing agent and loaded for electrophoresis on SDS-PAGE gel at room temperature, and the above-mentioned steps were carried out with minimum exposure to light. The biotinylated cysteines were immunoblotted with 3 μg/ml anti-biotin (Pierce) following the Western blot procedure described above.

The Saville method (30) was also used to biochemically detect the formation of S-nitrosothiol adducts on cysteine residues in the hOgg1-1a protein. The Saville method works on the principle that protein S-nitrosylation adducts replace with mercuric ions will react with sulfanilamide under acidic conditions to produce a diazoin salt. The formation of this salt can be monitored...
spectrophotometrically after its reaction with the aromatic amine (N-(1-naphthal-ethyl)-ethylenediamine) using an absorbance maxima of 540 nm (ε = 50,000 M⁻¹ cm⁻¹). Purified hOgg1-1a protein was treated with NO generated from 100 mM SNOC (30 min) and 300 μM SNAP (2 h) and peroxynitrite generated from 20 μM SIN-1 (1 h), using ultrafiltration cups as described above. As demonstrated previously (11, 12, 31), approximately 60–80 μM nitrite/nitrate is generated by this treatment. This method prevents contamination of the target protein solution with decomposition byproducts of SNAP, SNOC, and SIN-1. To 1 mg/ml purified hOgg1-1a protein in 100 mM Tris-Cl (pH 6.8) buffer, an equivalent volume of 1% sulfanilamide dissolved in 0.4 M HCl or an equivalent volume of 0.2% HgCl₂ in 1% sulfanilamide dissolved in 0.4 M HCl was added. The protein solution was incubated at room temperature for 10 min and mixed with an equal volume of a 0.02% solution of N-(1-naphthal-ethyl)enediamine dihydrochloride dissolved in 0.4 M HCl (Gress reagent). The sample absorbance was then read spectrophotometrically between 400 and 700 nm. The S-nitrosylation of the protein was quantified as the difference in absorbance between solution with HgCl₂, subtracted from one without HgCl₂. The experimental results were standardized with glutathione (γ-Glu-Cys-Gly) as described previously (32).

Quantification of Zinc Release from Purified hOgg1-1a. Approximately 500 μg of hOgg1-1a protein was immunoprecipitated from hOgg1-1a-transfected KMBC cells in 100 mM Tris-Cl (pH 7.0). Gaseous NO was applied to the protein solution through ultrafiltration cups with a M₉, 10,000 nominal molecular weight cutoff (Ultrafree-MC; Millipore) as described above. SNAP, freshly prepared SNOC, and SIN-1 were used. SNOC (100 mM) was prepared fresh from an equimolar solution of 100 mM sodium nitrite (NaNO₂) and 100 mM cysteine hydrochloride as described previously (31). To maintain optimum distance of 2 mm (head space gas volume) between target protein on the cellulose membrane and NO-producing chemicals in the filtrate, 400 μl of 300 μM SNAP or 100 mM SNOC or 20 μM SIN-1 solution was used. The cup was closed and incubated for 30 min (SNOC), 2 h (SNAP), and 1 h (SIN-1), respectively, at 4°C. After incubation, the protein solution was filtered by centrifugation (30 min at 5000 × g) to remove protein. The zinc concentrations in the filtrate were determined by monitoring the complexation of Zn⁺ with PAR at A₅₀₀nm using ZnSO₄ as standards as described previously (31).

RESULTS

Can hOgg1-1a Protein Be Expressed in and Immunoprecipitated from KMBC Cells? A HA epitope-tagged hOgg1-1a cDNA expression vector was transfected into KMBC cells, and the protein expression was assayed by both single cell immunofluorescence and immunoblot analysis 48 h later. As assessed by single cell immunofluorescence, transfected KMBC cells expressed the hOgg1-1a protein, which was detected exclusively in the nucleus (Fig. 1A); thus, the HA-tagged hOgg1-1a protein was expressed and appropriately localized in the nucleus of transfected cells. We had previously established that these cells express iNOS and generate NO after stimulation with a cytokine mixture (11, 12). To ensure that cytokines did not influence the expression of hOgg1-1a, we transfected cells in the presence of these compounds. Cytokine mixture and 1400W, a specific iNOS inhibitor, had no effect on hOgg1-1a protein expression after transfection with SNOC, SNAP, and SIN-1, a chemical that releases NO and superoxide (which combine to form peroxynitrite). When the enzyme was exposed to SNAP or SIN-1, its activity was inhibited. However, when C-PTIO, a NO scavenger, was added to the enzyme buffer, activity was preserved (Fig. 3, A and B). MnTBAP, a superoxide mimic, was also effective in preventing inhibition of enzyme activity during treatment with SIN-1 (Fig. 3B). The results suggest that either NO or peroxynitrite is capable of inhibiting the BER activity of hOgg1.

Does NO Directly Nitrosylate hOgg1-1a? An immunoblot assay was initially used to detect sites of NO-thiols on the hOgg1 protein. This assay labels these sites with Biotin-HDPP. Immunoblot analysis for Biotin-HDPP on hOgg1-1a identified S-nitrosothiol sites on the protein from both cytokine- and SNAP-treated cells. The nitrosylation of hOgg1 was NO dependent in the cytokine-treated cells because 1400W prevented labeling. Immunoprecipitated hOgg1-1a was treated with SNOC, SNAP, and SIN-1, and the number of S-nitrosothiol adducts was determined using the Saville reaction. Approximately 0.24, 0.30, and 0.17 μM S-nitrosothiol adducts form per milligram of purified hOgg1-1a protein after treatment with SNOC, SNAP, and SIN-1, respectively (Fig. 4B). Control experiments with untreated protein demonstrated that essentially no S-nitrosothiol adducts were formed. Thus, NO is capable of directly nitrosylating hOgg1.

Is NO-mediated S-Nitrosylation of hOgg1-1a Accompanied by Loss of Zn⁺? Free zinc released from immunoprecipitated hOgg1-1a protein was assayed using the metallochromic indicator PAR. This compound, when complexed to zinc, produces a visible PAR. This compound, when complexed to zinc, produces a visible

DISCUSSION

The results of the current study relate to NO-mediated inhibition of BER by hOgg1. The results demonstrate that (a) NO generated via cytokine induction of iNOS results in loss of hOgg1-1a BER activity, (b) hOgg1-1a enzyme activity can be directly inhibited by NO and peroxynitrite donors in a cell-free system, and (c) NO donors result in the formation of hOgg1-1a S-nitrosothiol adducts and loss of protein-bound zinc ions. The current studies suggest NO directly nitrosylates hOgg1, a reaction that causes loss of bound zinc and irreversible loss of enzyme activity. In conjunction with our previous studies (11, 12),
these results provide strong biochemical data to further implicate NO as an inhibitor of cellular BER activity.

We have previously shown that proinflammatory cytokines inhibit BER activity in cholangiocytes and cholangiocarcinoma cells by a NO-dependent process. The current study significantly extends these observations by identifying hOgg1 as a molecular target for NO inhibition of BER activity. Furthermore, the data provide mechanistic insight into NO-mediated inhibition of hOgg1 activity. Studies by others have shown that NO can reversibly or irreversibly inhibit their catalytic activity (21, 33, 34). NO inhibition of glycosylases has been attributed to S-nitrosothiol and 3-nitrotyrosine adduct formation (22, 35). The present data demonstrate the formation of S-nitrosothiol adducts in hOgg1-1a protein after treatment with NO donors. In contrast, 3-nitrotyrosine residues could not be detected by immunoblot analysis in the experimental paradigms used (data not shown). The formation of these S-nitrosothiol adducts was also associated with the loss of zinc ions from the protein. The release of zinc ions measured in response to S-nitrosothiol formation strongly suggests that loss of the active site cysteine 4-type zinc finger motif causes irreversible loss of hOgg1 tertiary structural integrity and hence loss of enzyme function.

The present findings suggest that either NO or peroxynitrite may inhibit hOgg1. For example, SNAP, a pharmacological NO donor, and SIN-1, a peroxynitrite donor, both inhibited hOgg1 activity. These results were bolstered by showing that C-PTIO, a NO scavenger, and MnTBAP, a peroxynitrite scavenger, protected the enzyme from loss of activity by SNAP and SIN-1, respectively. These results indicate that NO generation during inflammation may be sufficient to inhibit
repair activity, but peroxynitrite generated from NO and superoxide in
inflamed tissues may also contribute to inhibition of this enzyme.
Scavengers for both reactive nitrogen species are therefore expected
to help preserve base excision DNA repair activity in chronic inflam-
atory diseases.

We acknowledge that our results are based largely on in vitro
biochemical assays. Optimally, a specific assay for hOgg1 activity in
living cells would be ideal to confirm these observations. However, a
robust assay specific for specific hOgg1 activity in living cells has not
been developed and is difficult to conceive, given current technolog-
ical limitations. Therefore, extrapolation of our data to tissues in vivo
must take these considerations into account.

The hOGG1 gene maps to chromosome 3p26.2. This region shows
loss of heterozygosity in a variety of human cancers accompanied by
frequent GC→TA transversions and may therefore function as a
tumor repressor (15, 18, 36). Mutations in the hOGG1 gene have also
been identified in gastric cancer (37) and in lung and kidney tumors
(38), further suggesting that loss of hOgg1 function contributes to the
carcinogenesis process. Our previous studies, along with the current
findings, suggest that in addition to mutations in the hOGG1 gene,
posttranslational modification of hOgg1 may also contribute to the
initiation, promotion, and progression of human cancers. The latter
mechanisms may be especially important in chronic inflammatory

Fig. 2. NO generated from increased iNOS expression after cytokine stimulation
inhibits BER activity of hOgg1-1a. 8-oxodG-specific BER activity is assayed by recog-
nition and excision of the 8-oxodG lesion from the 24-bp oligonucleotide giving the 15-bp
cleaved product. A. WCEs from untransfected and hOGG1-1a-transfected cells exhibited
efficient BER activity. Incubation with cytokine mixture or 300 μM SNAP for 24 h after
transfection resulted in an inability to excise the 8-oxodG lesion. Coincubation with 50 μM
1400W or 10 mM DTT resulted in efficient excision activity. B. hOgg1-1a protein was
isolated from cells that were incubated with cytokine mixture ± 50 μM 1400W by HA-IP.
BER activity of purified hOgg1-1a protein was inhibited in cells incubated with cytokine
mixture and normal in cytokine ± 1400W-treated cells.

Fig. 3. NO and peroxynitrite generated from chemical donors inhibit BER activity of
hOgg1-1a. 8-oxodG-specific BER activity is assayed by recognition and excision of the
8-oxodG lesion from the 24-bp oligonucleotide giving the 15-bp cleaved product. Form-
amidopyrimidine glycosylase (Fpg), a bacterial 8-oxodG DNA-glycosylase, was used as
control. A, hOgg1-1a isolated by HA IP from KMBC cell lysates and exposed to NO from
300 μM SNAP did not excise the 8-oxodG lesion. This inhibition was ineffective in the
presence of C-PTIO but not MnTBAP. B, hOgg1-1a protein exposed to peroxynitrite
generated from 20 μM SIN-1 had inhibited BER activity that was reversed in the presence
of MnTBAP and C-PTIO.

Fig. 4. hOgg1 can be directly nitrosylated by NO and/or ONOO⁻. A, cells were
transfected with HA-hOgg1 and then treated with SNAP (300 μM), cytokine mixture, and
cytokine mixture plus 1400W (50 μM) for 24 h. Cell lysates were then obtained, and the
HA-tagged hOgg1 protein was immunoprecipitated. Sites of nitrosothiol adducts were
labeled with Biotin-HPDP as described in “Materials and Methods.” The protein was
separated by PAGE. The Biotin-HPDP-labeled sites were identified by an immunoblot
assay. Purified hOgg1-1a protein isolated from control cells and cells treated with 300 μM
SNAP, cytokine mixture, and cytokine mixture ± 50 μM 1400W was subjected to
S-nitrosylation assay, resolved by SDS-PAGE, and immunoblotted with an antibiotin
antibody. Only S-nitrosylated hOgg1-1a protein was capable of producing a signal in this
assay. B, S-nitrosothiol adducts in hOgg1-1a were detected following a modified Saville
method as described in “Materials and Methods.” Purified hOgg1-1a protein did not
contain any measurable amounts of S-nitrosothiols. Exposure of the protein to NO
generated from 300 μM SNAP for 2 h and 100 mM SNOC for 30 min resulted in a
significant amount of S-nitrosothiol adducts. Formation of peroxynitrite with 20 μM SIN-1
(1 h) also generated S-nitrosothiol adducts to a lesser extent.

Fig. 5. S-Nitrosothiol adducts in hOgg1-1a are accompanied by loss of zinc. A
colorimetric procedure was used to detect the PAR-Zn complex formed after the release
of zinc from hOgg1-1a. Exposure of the protein to NO generated from 300 μM SNAP for
2 h and 100 mM SNOC for 30 min resulted in the release of a significant amount of free
zinc. Formation of peroxynitrite with 20 μM SIN-1 (1 h) also caused the release of zinc.
diseases in which iNOS is induced and relatively high concentrations of NO are generated. This concept suggests that iNOS inhibition would have merit as a chemopreventive strategy to decrease cancer development in chronic inflammatory diseases of the biliary tract and perhaps in other organs as well. Chemopreventive approaches may include inhibition of iNOS expression with minocycline (39), inhibition of iNOS activity with selective nontoxic inhibitors (40, 41), or administration of NO scavengers (42). Animal models of carcinogenesis and cancer progression in wild-type and iNOS knockout animals coupled with studies of BER activity of hOgg1 will be useful to further test these concepts.

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