To identify the cellular gene target for Tat, we performed a gene expression profile analysis and found that Tat up-regulates the expression of the OGG1 (8-oxoguanine-DNA glycosylase-1) gene, which encodes an enzyme responsible for repairing the oxidatively damaged guanosine, 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG). We observed that Tat induced OGG1 gene expression by enhancing its promoter activity without changing its mRNA stability. We found that the upstream AP-4 site within the OGG1 promoter is responsible and that Tat interacted with AP-4 and removed AP-4 from the OGG1 promoter by in vivo chromatin immunoprecipitation assay. Thus, Tat appears to activate OGG1 expression by sequestrating AP-4. Interestingly, although Tat induces oxidative stress known to generate 8-oxo-dG, which causes the G:C to T:A transversion, we observed that the amount of 8-oxo-dG was reduced by Tat. When OGG1 was knocked down by small interfering RNA, Tat increased the amount of 8-oxo-dG, thus confirming the role of OGG1 in preventing the formation of 8-oxo-dG. These findings collectively indicate the possibility that Tat may play a role in maintenance of the genetic integrity of the proviral and host cellular genomes by up-regulating OGG1 as a feed-forward mechanism.

Tat is an essential transactivator of human immunodeficiency virus (HIV)1 gene expression and viral replication (1). Tat stimulates viral gene expression by directly binding to the characteristic RNA stem-loop-bulge structure called the transactivation response region located within the long terminal repeat (2, 3) and enhancing the processivity of RNA polymerase II (4, 5). The transcriptional activity of Tat is supported by interaction with cellular factors such as positive transcription elongation factor-b complex, binds to the activation domain of Tat and facilitates the hyperphosphorylation of the C-terminal domain of RNA polymerase II at the vicinity of HIV genes. Thus, Tat makes RNA polymerase II highly competent for the transcription elongation and productive expression of HIV genes (10).

Although much of the efforts in Tat studies have focused on its transcriptional activation from the HIV provirus, the actions of Tat on cellular genes have also been revealed. For example, Tat is known to promote cellular transformation (11), to induce oxidative stress (12, 13), and to elicit inflammatory reactions (14, 15). Choi et al. (16) observed that Tat transgenic mice exhibit decreased gene expression of the γ-glutamylcysteine synthetase regulatory subunit and decreased GSH content in tissues. These biological actions of Tat are considered to cause activation of nuclear factor-κB, AP-1 (activating protein-1), and mitogen-activated protein kinase (13, 17). These findings prompted us to search for cellular target genes of Tat, either up-regulated or down-regulated, using a gene expression profile analysis.

In addition to the very high efficiency of the viral replication rate that is mainly ascribable to Tat action, HIV owes its morbidity to its high mutation rate, leading to the emergence of drug resistance and escape from the host immune response. In fact, the high frequency of G:C to A:T and G:C to T:A mutations was previously observed in HIV-1 and other lentiviruses (18–21). Recent studies (22–25) have deciphered one such mechanism that involves the HIV-encoded virion infectivity factor blocking the enzymatic activity of cytidine deaminase CEM15 (also known as APOBEC3G for apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G), which induces G:C to A:T hypermutation in newly synthesized DNA. Another type of mutation, G:C to T:A transversion, is mediated by the generation of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) by radical oxygen species (ROS) and occurs at the DNA level (26, 27). The oxidatively damaged guanosine, 8-oxo-dG, is widely accepted as a pre-mutagenic lesion because of its potential to mispair with adenine, thus generating the G:C to T:A transversion. This type of mutation is often found in tumor suppressor genes and oncogenes, such as p53 and K-ras, in mammalian cells (28, 29). The OGG1 (8-oxoguanine-DNA glycosylase-1) enzyme is responsible for the excision/repair of this oxidatively damaged DNA by excising 8-oxo-dG (30–32). In fact, OGG1 gene knockout actually shows accumulation of such a mutation (33, 34).

In this study, we demonstrate the up-regulation of OGG1 by Tat and provide evidence that this effect of Tat is through the sequestration of the negative transcription factor AP-4 for the expression of OGG1. We examine the effect of Tat on the actual
levels of 8-oxo-dG in the presence and absence of small interfering RNA (siRNA) against OGG1 mRNA.

**EXPERIMENTAL PROCEDURES**

Plasmids—The cDNA of wild-type Tat (101 amino acids) originating from HIV-1 was amplified by PCR with the oligonucleotide primer pair 5'-GGG GAG CCG CCA CCA TGG ATT ACA AGG ATG ATG AGC ATG AGA AGA CAG CGC CAC TGG TAT ACA AGG ATG AAG GAC AGT CAC TGC TGT CCG TAT CCA-3' (forward; containing an EcoRI site and a FLAG epitope) and 5'-GGC GAA TCT CGG ATG ACG CGG CTG ATG TCT AGC TCT CTC-3' (reverse; containing a BamHI site). The amplified DNA fragment was digested with EcoRI and BamHI and ligated in-frame into the pIND-V5 expression vector (Invitrogen), thus generating pIND-Tat. As a control, we employed mutant Tat (mTat) lacking transcriptional activity because of the absence of binding activity with cyclin T1 or the transactivation response region (6–8). The plasmid expressing mutant Tat (pIND-mTat) in which Cys20 and Lys41 were substituted with Ala was generated using a QuikChange site-directed mutagenesis kit (Stratagene) with the following mutagenic oligonucleotide primer pairs: 5'-CTA TTG TAA AAG GGC CTG CTT CTA TTG CC-3' (forward) and 5'-GGG CAA GGC CCT TTA TAC AAT AG-3' (reverse) or 5'-GGT TCA GAG GGA GCC CGA GCA TCT GAT-3' (forward; containing an EcoRI site) and 5'-GGT CTA GAG GGA GCC CGA GCA TCT GAT-3' (reverse). To generate the mammalian expression plasmid for AP-4, AP-4 gene was amplified by PCR with the oligonucleotide primer pair 5'-GGG GAG CCG CCA CCA TGG ATT ACA AGG ATG AAG GAC AGT CAC TGC TGT CCG TAT CCA-3' (forward; containing an EcoRI site) and 5'-GGC GAA TCT CGG ATG ACG CGG CTG ATG TCT AGC TCT CTC-3' (reverse; containing a BamHI site). The amplified DNA fragment was digested with EcoRI and BamHI and ligated in-frame into the pcDNA-Myc expression vector (Invitrogen). The construction of pCD12-luc, containing the HIV-1 long terminal repeat V3 and R linked to the luciferase gene, and pcDNA-Tat was described previously (35, 36). Human OGG1 promoter-luciferase fusion constructs, including pPR-116, pPR-128, and pPR-143, were kindly provided by Dr. J. P. Radicella (Radiobiologie Moleculaire et Cellulaire, CNRS-CEA, Fontenay aux Roses, France) (37). The mutant pPR-128-luc reporter constructs were generated using a QuikChange site-directed mutagenesis kit. The mutant sequences (sense strand) utilized were as follows: 5'-AP-4 site mutant (m5-AP-4), GAC GGC AGG CAG leg cga TGG CGG CCG CGG; 3'-AP-4 site mutant (m3-AP-4), GGG AAA GGG GAG GCG TCC cgr cga GCA GAG ACC CCA G; GA TA site mutant (mGATA), CTT GCA GCC TAT TGA TTA AGC ACG; and AP-2 site mutant (mAP-2), CAG CTG TCG GGG CCG Cca ttC GGG ACG ACA ATC (with consensus binding sites underlined and mutated sequences in lowercase letters). The construct containing mutations in both the 5'- and 3'-AP-4 sites (mAP-4) was generated by two successive PCRs using the m5-AP-4 and m3-AP-4 mutant sequences. The control luciferase reporter plasmid pG3-LucBasic vector was purchased from Promega. All constructs were verified by sequencing. The primers used are listed in Table I. The pcDNA3.1(+)/EGFP PRISM™ dye terminator cycle sequencing ready kit (PerkinElmer Life Sciences) on an Applied Biosystems 313 Automated DNA Sequencer. Analysis of differential expression of each gene was performed using SuperSignal (Pierce). To evaluate the level of OGG1 protein, cells were similarly treated with lysis buffer, and the antibody-bound proteins were dissolved by boiling in 2× Laemml sample buffer. After centrifugation, the supernatant proteins were separated by SDS-PAGE and transferred to nitrocellulose membrane (Hybond-C, Amersham Biosciences). The membrane was probed with antibodies, including anti-OGG1 (Santa Cruz Biotechnology Inc.), anti-FLAG (Sigma), and anti-Myc (Santa Cruz Biotechnology Inc.), anti-AP-4 (Cell Signaling), and anti-AP-1 (Santa Cruz Biotechnology Inc.) antibodies; and immunoreactive proteins were visualized by enhanced chemiluminescence (SuperSignal, Pierce). To evaluate the levels of Tat proteins, the microarray slide was washed three times (2 h after PNA stimulation in 293/Tat and 293/LacZ cells) and two times (12 h after PNA stimulation in 293/Tat and 293/LacZ). The luciferase activity was normalized to Renilla luciferase activity as an internal control to assess the transfection efficiency. The data are presented as the fold increase in luciferase activities (means ± S.D.) relative to the control from three independent transfections.

**Reverse Transcription (RT)-PCR**—For cDNA synthesis, 1 μg of purified total RNA were reverse-transcribed using oligo(dT) primer and SuperScript II reverse transcriptase. The cDNA was then amplified from each RNA sample with Taq PCR Master Mix (Qiagen Inc.) and gene-specific primers designed using Oligo Version 4.0 software (Molecular Biology Insights). The primer sequences for each amplified gene are listed in Table II. PCR products were separated on 1.5% agarose gels (Sigma), blotted onto nylon membranes (Amersham Pharmacia Biotech), and hybridized with the antisense gene-specific oligonucleotides (5'-CCA GCA GGA AAT ACG AAG AAA TGA TGA-3' (reverse); forward) and 5'-GAA TAC GGG CTA AAC AAG AAA TGA TGA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward) or 5'-GCC TGC CCA AGG ACT TCC AGC-3' (forward) and 5'-CCA GTG ATG CCG GAG TGT TTA-3' (reverse); forward). The mRNA samples were digested with RNase-free Dnase, ethanol-precipitated, and further purified through Microcon YM-100 columns (Amicon Inc.). The quantity and quality of mRNA were assessed by capillary electrophoresis using an Agilent 2100 bioanalyzer.

**Generation of Fluorescently Tagged cDNA and Gene Expression Profile Analysis**—Gene expression profiles were examined as described (39, 40) using the human 3K DNA CHIP34 (Takara) containing 2800 human genes of known functions. Briefly, fluorescently labeled cDNA was synthesized from 1-μg aliquots of purified mRNA by oligo(dT)-primed polymerization using SuperScript II reverse transcriptase (Invitrogen). The pool of nucleotides in the labeling reaction contained 0.5 mM each of dTTP, dATP, and dGP; 0.3 mM dCTP; and 0.1 mM fluorescent nucleotide (Cy3- or Cy5-labeled dCTP, Amersham Biosciences). Fluorescently labeled cDNA was purified by chromatography through Microcon YM-20 columns (Amicon Inc.). The microarray slide was hybridized to combined Cy5-dCTP- and Cy3-dCTP-labeled cDNA probes for 14 h in hybridization solution (6× SSC and 0.2% SDS with 5× Denhardt's solution and carrier DNA) at 65 °C under coverslips. After hybridization, the microarray slide was washed twice with 1.2× SSC and 0.2% SDS at 55 °C for 5 min, with 1.2× SSC and 0.2% SDS at 65 °C for 5 min, and with 0.05× SSC at room temperature as a final wash. The hybridized array was scanned at 10-μm resolution on an Affymetrix 428 array scanner. Analysis of differential expression of each gene was performed using ImaGene Version 4.2 computer software (Bio-Discovery Ltd.). Normalization of hybridized signals was performed by global scaling. These experiments were repeatedly performed: we performed comparative microarray analyses three times (24 h after PNA stimulation in 293/Tat and 293/LacZ cells) and two times (12 h after PNA stimulation in 293/Tat and 293/LacZ cells).
**Induction of OGG1 by Tat**

**Measurement of Manganese Superoxide Dismutase Activity**—The enzyme activity of manganese superoxide dismutase was measured using a WST-1™ superoxide dismutase assay kit (Dojindo) with slight modifications. Briefly, equal numbers of cells (1.5 x 10⁷) were washed twice with PBS, and the cell lysates were extracted by freeze/thawing.

The manganese superoxide dismutase activity in the supernatant protein lysate was determined by incubation with WST-1, xanthine, and xanthine oxidase at 37 °C for 20 min. To mask the enzyme activity, one unit of superoxide dismutase activity, the protein lysate was treated with 1 mM KCN. The inhibitory action of manganese superoxide dismutase contained in each cell lysate was assessed by the spectrophotometric determination of WST-1 formazan at 450 nm. Quantification was achieved by comparison with the absorption of standard manganese superoxide dismutase ( Sigma) with known concentrations.

**Electrophoretic Mobility Shift Assay**—The experimental procedure was carried out as described previously (36). The AP-4 consensus sequence was taken from the 5'-AP-4 site in the OGG1 promoter.

The wild-type and mutant oligonucleotide sequences (sense strand) utilized were as follows: wild-type, 5'-CCG CAG GCA GGT GTC GCG AG-3'; and mutant, 5'-CCG CAG GCA GGT GTC GCG AG-3'. These oligonucleotides were labeled using a 5'-end labeling kit (Takara) in the presence of γ-²⁵³⁵ P ATP. DNA binding reactions were performed at 4 °C for 20 min in a 10-µl reaction volume. Analysis of binding complexes was performed by electrophoresis on 6% polyacrylamide gels with 0.5 × Tris borate/EDTA buffer, followed by autoradiography. The specificity of DNA binding was assessed by preincubating extracts with anti-AP-4 antibody and competitor at room temperature for 10 min.

**ChIP assay**—The ChIP procedure was carried out as described previously (36). The AP-4 consensus sequence was taken from the 5'-AP-4 site in the OGG1 promoter.

The wild-type and mutant oligonucleotide sequences (sense strand) utilized were as follows: wild-type, 5'-CCG CAG GCA GGT GTC GCG AG-3'; and mutant, 5'-CCG CAG GCA GGT GTC GCG AG-3'. These oligonucleotides were labeled using a 5'-end labeling kit (Takara) in the presence of γ-²⁵³⁵ P ATP. DNA binding reactions were performed at 4 °C for 20 min in a 10-µl reaction volume. Analysis of binding complexes was performed by electrophoresis on 6% polyacrylamide gels with 0.5 × Tris borate/EDTA buffer, followed by autoradiography. The specificity of DNA binding was assessed by preincubating extracts with anti-AP-4 antibody and competitor at room temperature for 10 min.

**Caspase 3 Monoclonal Antibody—**Caspase 3 was performed according to the manufacturer's instructions (R&D Systems). The specificity of antibody was assessed by Western blotting.

**ChIP assay**—The ChIP procedure was carried out as described previously (36). The AP-4 consensus sequence was taken from the 5'-AP-4 site in the OGG1 promoter.

The wild-type and mutant oligonucleotide sequences (sense strand) utilized were as follows: wild-type, 5'-CCG CAG GCA GGT GTC GCG AG-3'; and mutant, 5'-CCG CAG GCA GGT GTC GCG AG-3'. These oligonucleotides were labeled using a 5'-end labeling kit (Takara) in the presence of γ-²⁵³⁵ P ATP. DNA binding reactions were performed at 4 °C for 20 min in a 10-µl reaction volume. Analysis of binding complexes was performed by electrophoresis on 6% polyacrylamide gels with 0.5 × Tris borate/EDTA buffer, followed by autoradiography. The specificity of DNA binding was assessed by preincubating extracts with anti-AP-4 antibody and competitor at room temperature for 10 min.

**Measurement of Intracellular Reduced GSH and GSSG Contents**—The total cellular GSH and GSSG concentrations were measured using a high performance liquid chromatography (HPLC)-electrochemical detector (ECD) system, which is highly selec-
Introduction of OGG1 by Tat

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**Results**

**Establishment and Characterization of Ecdysone-inducible Cell Lines Expressing Tat and mTat**—Because Tat is known to impair cell viability and its activity in long-term maintenance of cells expressing Tat may preselect certain cell types and preclude exploration of the Tat-mediated alteration of cellular functions, we adopted a stringent ecdysone-inducible system using PnA, a phytocerebrosterol that is inert in mammals (45). To generate Tat- or mTat-expressing cells upon treatment with PnA, we transfected the pIND-Tat or pIND-mTat plasmid into 293T cells without (control) and with PnA treatment. The cDNA expression of Tat and mTat was confirmed by real-time RT-PCR together with the amounts of HIV-1 p24 antigen produced in the culture supernatant. As shown in Fig. 3B, OGG1 gene expression was up-regulated by 3.6-, 6.7-, 9.8-, and 8.2-fold upon Tat expression after 6, 12, 24, and 48 h of PnA treatment, respectively. mTat did not affect OGG1 mRNA upon Tat expression after 6, 12, 24, and 48 h of PnA treatment.

**Induction of OGG1 Gene Expression by Tat**—Because Tat up-regulated the OGG1 gene the most, we further analyzed the effect of Tat on OGG1 mRNA expression and stability. The human OGG1 gene encodes two isoforms, type 1 (a and b) and type 2 (a, b, and c), resulting from alternative splicing of the single OGG1 precursor mRNA (51). As shown in Fig. 3A, Tat induced all types of OGG1 mRNA. We carried out real-time RT-PCR to determine more precisely the mRNA levels of OGG1 before and after Tat induction. As shown in Fig. 3B, OGG1 gene expression was up-regulated by 3.6-, 6.7-, 9.8-, and 8.2-fold upon Tat expression after 6, 12, 24, and 48 h of PnA treatment, respectively. mTat did not affect OGG1 gene expression (Fig. 3B). A similar extent of stimulation was observed for OGG1 protein levels as revealed by Western blotting (Fig. 3C). No induction of OGG1 protein was observed when mTat was induced. Induction of OGG1 protein by Tat (but not mTat) was confirmed in Jurkat T cells, a natural host of HIV-1 infection (Fig. 3C, right panels). Furthermore, the effect of HIV-1 infection on OGG1 gene expression was examined with PBMCs isolated from two individuals and Jurkat cells. These cells were infected with HIV-1MN, and the OGG1 mRNA level was quantified by real-time RT-PCR together with the amounts of HIV-1 produced in the culture supernatant. As shown in Fig. 3D, up-regulation of OGG1 mRNA levels upon HIV-1 infection was observed and was associated with elevation of viral p24 antigen levels. Mock infection did not induce OGG1 expression (data not shown).

Furthermore, we examined the effect of Tat on the stability of OGG1 mRNA using PnA-inducible cells. After 24 h of Tat or mTat induction, cells were treated with actinomycin D, and total RNA samples were obtained after 1, 3, 5, and 7 h of actinomycin D treatment to determine the level of OGG1 mRNA. As shown in Fig. 3E, the decay profiles of OGG1 mRNA were similar in cells expressing Tat and mTat (control), with half-lives of 5.0 and 4.3 h, respectively. These findings indicate that the positive effects of Tat on OGG1 gene expression are at the level of transcription.

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**Gene Expression Profile Analysis of Cells Expressing Tat**—To identify genes either up-regulated or down-regulated by Tat in the newly established ecdysone-inducible cell lines, the gene expression profiles were compared with and without Tat expression. The mRNA was isolated from Tat/293 cells and control cells without (control) and with PnA treatment. The cDNA probes were synthesized from each mRNA, labeled with Cy5 (for Tat- or LacZ-expressing cells) or Cy3 (for non-expressing control), and hybridized to a gene chip (human 3K DNA CHIP™). Representative results are shown in Fig. 2A, where we compared gene expression in Tat-expressing (Cy5-labeled) and non-expressing control (Cy3-labeled) 293/Tat cells. Similar comparisons were made with LacZ-expressing cells (data not shown).

As shown in Fig. 2A, 12 genes, including TFP21, stanniocalcin-1, SEPP1, and OGG1, were up-regulated by >2-fold by Tat after 24 h of induction upon PnA treatment. Five of these 12 genes were up-regulated by >2-fold even after 12 h of Tat induction. The details of these genes are summarized in Table I. In control LacZ/293 cells, expression of the TFP21 gene was up-regulated by 2.0-fold when cells were treated with PnA, suggesting nonspecific stimulation by PnA (data not shown).

On the other hand, eight genes were down-regulated to <60% after 24 h of Tat induction (summarized in Table I). Down-regulation of these genes was not observed in LacZ-expressing cells (data not shown).

To confirm these results, we carried out RT-PCR analysis to examine the mRNA levels of Tat-regulated genes before and after Tat induction. We also examined the effect of mTat to further confirm the specificity of Tat action. Fig. 2B shows the results of eight genes up-regulated by Tat by >2.3-fold (stanniocalcin-1, SEPP1, OGG1, MEN1, homolog FLJ23538/clone 137308, ENPP2, and TFP21). Among these genes, stanniocalcin-1, SEPP1, and ENPP2 were also up-regulated by induction of mTat or even LacZ, suggesting a nonspecific effect of PnA. Thus, we concluded that five genes (OGG1, MEN1, homolog FLJ23538/clone 137308, integrin a7, SLC20A1, and ENPP2) are specifically up-regulated by Tat because these genes were not up-regulated by either mTat or LacZ. Whereas ENPP2 was up-regulated after 12–24 h of Tat induction and subsequently down-regulated, the other four genes were constitutively up-regulated.

Similarly, RT-PCR analysis was performed with the eight genes down-regulated by Tat (Fig. 2C). Two of the genes (SLC1A3 and LTA1) were down-regulated by mTat or LacZ. The other six were down-regulated by Tat, but not by mTat or LacZ. Among the genes down-regulated by Tat, RGS16, and hexokinase-2 are known to be under the transcriptional control of p53 (46–48), an observation consistent with previous reports of Tat down-regulating the action of p53 (49, 50).

Induction of OGG1 Gene Expression by Tat—Because Tat up-regulated the OGG1 gene the most, we further analyzed the effect of Tat on OGG1 mRNA expression and stability. The human OGG1 gene encodes two isoforms, type 1 (a and b) and type 2 (a, b, and c), resulting from alternative splicing of the single OGG1 precursor mRNA (51). As shown in Fig. 3A, Tat induced all types of OGG1 mRNA. We carried out real-time RT-PCR to determine more precisely the mRNA levels of OGG1 before and after Tat induction. As shown in Fig. 3B, OGG1 gene expression was up-regulated by 3.6-, 6.7-, 9.8-, and 8.2-fold upon Tat expression after 6, 12, 24, and 48 h of PnA treatment, respectively. mTat did not affect OGG1 gene expression (Fig. 3B). A similar extent of stimulation was observed for OGG1 protein levels as revealed by Western blotting (Fig. 3C). No induction of OGG1 protein was observed when mTat was induced. Induction of OGG1 protein by Tat (but not mTat) was confirmed in Jurkat T cells, a natural host of HIV-1 infection (Fig. 3C, right panels). Furthermore, the effect of HIV-1 infection on OGG1 gene expression was examined with PBMCs isolated from two individuals and Jurkat cells. These cells were infected with HIV-1MN, and the OGG1 mRNA level was quantified by real-time RT-PCR together with the amounts of HIV-1 produced in the culture supernatant. As shown in Fig. 3D, up-regulation of OGG1 mRNA levels upon HIV-1 infection was observed and was associated with elevation of viral p24 antigen levels. Mock infection did not induce OGG1 expression (data not shown).

Furthermore, we examined the effect of Tat on the stability of OGG1 mRNA using PnA-inducible cells. After 24 h of Tat or mTat induction, cells were treated with actinomycin D, and total RNA samples were obtained after 1, 3, 5, and 7 h of actinomycin D treatment to determine the level of OGG1 mRNA. As shown in Fig. 3E, the decay profiles of OGG1 mRNA were similar in cells expressing Tat and mTat (control), with half-lives of 5.0 and 4.3 h, respectively. These findings indicate that the positive effects of Tat on OGG1 gene expression are at the level of transcription.
Induction of OGG1 Expression Is Not through the Oxidative Stress Induced by Tat—Because Tat is known to induce oxidative stress (12, 15, 17), it is possible that OGG1 induction might be an indirect effect of Tat, although it is not yet known whether oxidative stress induces OGG1 gene expression. We first examined whether Tat induces oxidative stress in Tat/293 cells. Fluorescence-activated cell sorter analysis with the oxidation-sensitive fluorescent probe 2',7'-dichlorofluorescein diacetate showed that Tat (but not mTat) increased the intracellular ROS levels (Fig. 4A). We measured the intracellular levels of GSH and GSSG. As expected, the content of GSSG, the oxidized form of GSH, was increased (~2.3-fold) in Tat-expressing cells in contrast to control mTat-expressing cells (Fig. 4B). The GSH (reduced form) level in Tat-expressing cells was decreased to 57% of that in control cells. No significant reduction in GSH was detected in mTat-expressing cells. Furthermore, the manganese superoxide dismutase activity was down-regulated by Tat as reported previously (12). After 24 h of Tat induction, the manganese superoxide dismutase activity was decreased to 59% (Fig. 4C).

These results led us to examine whether Tat-induced OGG1 gene expression is attributable to the oxidative stress associated with Tat action. However, treatment with antioxidants did not block Tat-mediated OGG1 induction (Fig. 4D). 293/Tat cells were pretreated with antioxidants, including pyrrolidine dithiocarbamate, N-acetyl-L-cysteine, epigallocatechin gallate (a phenolic antioxidant), and Trolox (a water-soluble vitamin E analog), prior to Tat induction (Fig. 4D, left panel). When the OGG1 mRNA was measured by real-time RT-PCR, Tat-induced OGG1 expression was not affected by the antioxidants. In
**FIG. 2. Gene expression profile analysis and confirmatory RT-PCR.**

A, scatter plot of the hybridization signal intensity of genes in cells expressing Tat versus control cells. The mRNA was isolated from Tat/293 cells without (control) or with PonA treatment for 24 h. The cDNA probes were synthesized from the mRNA of each cell culture and labeled with either Cy5 (for Tat-expressing cells) or Cy3 (for control 293 cells). These probes were hybridized, in combination, to a gene chip (human 3K DNA CHIP). The signal intensity of each gene on the microarray chip was
Induction of OGG1 by Tat

TABLE I
Genes up-regulated by Tat

| Gene            | Induction (fold) | GenBank accession no. |
|-----------------|------------------|-----------------------|
|                 | 12 h             | 24 h                  |
| TFPI2           | 6.5±0.3          | NM_006528             |
| Stanniocalcin-1  | 2.4 ± 0.3        | NM_003155             |
| SEPP1           | 2.4 ± 0.3        | NM_005410             |
| OGG1            | 2.6 ± 0.2        | NM_016819             |
| Human clone 137308 mRNA; similar to MEN1βd | 1.1 ± 0.2 | U60873 |
| ETV5 (Ets-related molecule) | 1.8 ± 0.2 | NM_004545 |
| Homo sapiens cDNA, similar to MEN1βd | 1.1 ± 0.2 | AK027191 |
| SLC20A1         | 1.8 ± 0.3        | NM_005415             |
| Integrin α7     | 1.9 ± 0.1        | NM_002206             |
| KRTP35a         | 1.7 ± 0.2        | NM_006209             |
| ABCG1 (ATP-binding cassette, subfamily G (WHITE), member 1) | 1.3 ± 0.1 | NM_004915 |
| Calcium-binding protein p22 | 2.1 ± 0.1 | BC001646 |
| Laminin α3      | 1.4 ± 0.1        | NM_000227             |

a Non-specifically up-regulated by PonA treatment (see Fig. 5 for the results of RT-PCR).  
b Data from single determinations 12 h after Tat induction.  
c Data from triplicate determinations 12 h after Tat induction (expressed as means ± S.D.).  
d Different cDNA segments of the same gene.

TABLE II
Genes down-regulated by Tat

| Gene            | Induction (fold) | GenBank accession no. |
|-----------------|------------------|-----------------------|
|                 | 12 h             | 24 h                  |
| NDRG1           | 0.5±0.1          | NM_006096             |
| ARIE            | 0.5±0.1          | NM_005168             |
| SLC1A3          | 0.7 ± 0.1        | NM_004172             |
| NTHL1           | 0.8 ± 0.1        | NM_002528             |
| HSTF2           | 0.5 ± 0.1        | NM_004506             |
| RGS16           | 0.7 ± 0.1        | NM_002928             |
| Hexokinase-2    | 0.7 ± 0.1        | NM_000189             |
| LAT1            | 1.3 ± 0.2        | AF104022              |

a Data from single determinations 12 h after Tat induction.  
b Data from triplicate determinations 24 h after Tat induction (expressed as means ± S.D.).  
c Non-specifically up-regulated by PonA treatment (see Fig. 6 for the results of RT-PCR).

addition, H2O2 and oxidative stress inducers such as inflammatory cytokines (tumor necrosis factor-α and interleukin-1β) and lipopolysaccharide could not up-regulate OGG1 gene expression (Fig. 4D, right panel). In support of these findings, when we performed transient luciferase assay using the OGG1 promoter construct, no OGG1 induction by these stimuli was observed (data not shown), consistent with a previous report by Dhénaut et al. (37). Therefore, it is unlikely that Tat induces OGG1 expression through ROS production.

Transactivation of OGG1 by Tat—These observations prompted us to examine the possibility that Tat-mediated OGG1 expression is the direct effect of Tat. We thus examined the effect of Tat on OGG1 promoter activity. The transient luciferase assay was performed on various regions of the OGG1 promoter linked to the luciferase reporter gene (Fig. 5A). As shown in Fig. 5A, Tat stimulated the transcripational activity of the reporter constructs containing the sequence upstream from position −472. Whereas the sequence upstream from position −945 was dispensable for Tat-mediated transactivation, no such effect was observed when the region spanning positions 945 to −472 was deleted (Fig. 5A, lower left panel). In 293 cells expressing mTat, no induction of OGG1 promoter activity (other than the constitutive transcriptional activity) was observed. We also examined the Tat-mediated transactivation of the OGG1 promoter in Jurkat cells and obtained essentially the same results (Fig. 5A, lower right panel).

Thus, Tat appears to transactivate OGG1 expression through transcription factors located within the OGG1 promoter region from positions −945 to −472. To further elucidate the mechanism by which Tat induces OGG1 transcription, we created specific mutants lacking binding sites for GATA, AP-4, and/or AP-2 located in this region. When AP-4 sites were mutated, Tat no longer augmented the promoter activity (Fig. 5B, black bars). However, no reduction in Tat-mediated transactivation was observed when other sites were mutated. In addition, the basal promoter activity was augmented when the 5′-AP-4 site was mutated, whereas mutation of the GATA, AP-2, and 3′-AP-4 sites had little effect on the basal OGG1 promoter activity (Fig. 5B, hatched bars), indicating that AP-4 acts as a transcriptional repressor of OGG1 expression. These results suggest that AP-4 sites are required for Tat-induced OGG1 gene expression and that the 5′-AP-4 site negatively regulates OGG1 gene expression. In fact, overexpression of AP-4 inhibited both the Tat-stimulated and basal levels of OGG1 gene expression without affecting the level of Tat expression (Fig. 5C).

Tat Interacts with AP-4 and Removes It from the OGG1 Promoter—To further investigate the mechanism by which Tat stimulates OGG1 gene expression, we first examined the effect of Tat on AP-4 DNA binding by electrophoretic mobility shift assay. As shown in Fig. 6A, constitutive AP-4 DNA binding was observed in the cells, and a significant reduction in AP-4 DNA binding was observed when Tat was induced by PonA treatment. No such effect was observed when mTat was expressed. We then examined whether Tat associates with AP-4 in cultured cells by co-immunoprecipitation with either Tat (FLAG epitope-tagged) or AP-4 (Myc epitope-tagged). As shown in Fig. 6B, when Tat was immunoprecipitated with anti-FLAG antibody, endogenous AP-4 protein was detected within the immune complex. No AP-4 was co-immunoprecipitated with mTat. Conversely, when AP-4 was immunoprecipitated with

Plotted. Genes with a signal intensity <200 U (of Cy5 and Cy3) were excluded from further analysis. Solid and dashed lines indicate the upper and lower boundaries of 1.5- and 2-fold changes, respectively. B and C, confirmation of genes up- or down-regulated by Tat using RT-PCR. B, genes up-regulated by Tat. Up-regulation of the stanniocalcin-1, SEPP1, and ETV5 genes observed in cDNA array analysis appeared to be unspcific. C, genes down-regulated by Tat. Down-regulation of the SLC1A3 and LAT1 genes was considered nonspecific. RT-PCR analysis was performed with gene-specific primers and total RNA prepared from Tat/293, mTat/293, and LacZ/293 cells. Each cell culture was treated with PonA (10 μM) for the indicated periods of time. N.D., not determined.
anti-Myc antibody, Tat (but not mTat) was co-immunoprecipitated (Fig. 6B, lower panels).

Furthermore, the ChIP assay was performed to examine whether the inhibition of AP-4 DNA binding by Tat occurs at the endogenous OGG1 gene promoter. Tat/293 and mTat/293 cells were transfected with plasmids expressing Myc-tagged AP-4 or Myc-tagged LacZ (control), stimulated with PonA to express Tat or mTat, treated with formamide, and sonicated, and the cross-linked protein-DNA complex was immunoprecipitated with specific antibodies recognizing the Myc (AP-4) or V5 (Tat) epitope. The immunoprecipitated DNA was analyzed by PCR using primer pairs for the AP-4-binding sites within the OGG1 promoter (−615 to −450). As demonstrated in Fig. 6C, a significant reduction in AP-4 bound to the OGG1 promoter DNA was observed, and the extent of reduction was proportionate to the amount of Tat expressed (corresponding to the time-dependent expression of Tat in Fig. 1). No such effect was observed when mTat was expressed. The antibody to Tat precipitated the OGG1 promoter (Fig. 6C, left panels), indicating that the Tat-AP-4-DNA ternary complex may be transiently formed. These observations indicate that Tat directly activates OGG1 gene expression through sequestrating AP-4, a negative transcriptional regulator of OGG1 expression.

Reduction of 8-Oxo-dG Levels by Tat and Effect of OGG1 Knockdown—Because OGG1 is responsible for the excision/repair of the oxidation-damaged DNA by excising 8-oxo-dG (30) and because Tat induces expression of OGG1, we measured the amounts of 8-oxo-dG in the cellular DNA by the HPLC-ECD method (26). Fig. 7A shows the levels of 8-oxo-dG before and after Tat expression. In control cells, the level of 8-oxo-dG was 8.7 ± 0.34 residues/10⁶ dG residues (Fig. 7B). However, upon expression of Tat, the 8-oxo-dG levels were reduced to 7.7 ± 0.89 (0.64-fold), 5.6 ± 0.30 (0.64-fold), and 4.5 ± 1.2 (0.52-fold) residues/10⁶ dG residues after 6, 12, and 24 h of Tat induction, respectively. Statistically significant reduction was observed after 12 and 24 h of Tat induction. No significant reduction in 8-oxo-dG levels was observed when mTat was expressed. Taken together, these observations indicate that Tat prevents accumulation of 8-oxo-dG by directly up-regulating OGG1 expression.

To confirm these findings, we adopted a siRNA technique to specifically knock down OGG1 mRNA and examined the effect of Tat on the level of 8-oxo-dG when endogenous OGG1 was
depleted. We synthesized three kinds of 21-nucleotide siRNA duplexes corresponding to the conserved OGG1 mRNA regions utilized in all types of OGG1 mRNA species. Cells transduced with OGG1 siRNA (No. 1) showed the greatest reduction in OGG1 protein levels compared with the control (Fig. 7C) and were thus used in the following experiment. As demonstrated
in Fig. 7D, OGG1 depletion by OGG1 siRNA (No. 1) resulted in a significant increase in the level of 8-oxo-dG (1.6-fold with the control and 1.4-fold with control siRNA). More important, 8-oxo-dG formation was induced by Tat when OGG1 was depleted (2.2-fold with the control and 1.9-fold with control siRNA). In addition, overexpression of AP-4, acting as a negative regulator of OGG1 expression, increased the level of 8-oxo-dG (1.8-fold with the control).

DISCUSSION

In this study, we have explored the biological effects of Tat using gene expression profile analysis. We found that (i) Tat induces the OGG1 gene and that (ii) Tat down-regulates the NDRG1, RSG16, and hexokinase-2 genes. The latter genes are known to be under the transcriptional control of p53 (46–48). Interestingly, Li et al. (49) observed the repression of p53 mRNA by Tat. Moreover, Tat was shown to directly inactivate p53 by protein-protein interaction (50, 52). Thus, the Tat-mediated down-regulation of these genes is consistent with previous findings. However, Tat-mediated OGG1 induction has not been reported. Thus, in this study, we analyzed the mechanism by which Tat induces OGG1 gene expression.

We found that Tat-mediated OGG1 induction is not through stabilization of the OGG1 mRNA. In addition, Tat-mediated OGG1 induction was not reversed by treatment with antioxidants, indicating that Tat-mediated OGG1 induction could not be attributable to oxidative stress induced by Tat. By performing transient luciferase assay using the reporter plasmid containing various regions of OGG1, we found that Tat expression (upper panel). The dose-dependent expression of AP-4 was revealed by Western blotting with anti-Myc tag antibody (lower panels). Tat protein expression was monitored using anti-FLAG antibody.
AP-4 site and that Tat activates *OGG1* promoter activity by sequestrating AP-4 from the *OGG1* promoter. Thus, the positive effect of Tat on *OGG1* gene expression appears to be a direct effect.

Intriguingly, we observed that the extent of oxidation-induced guanosine modification (8-oxo-dG) was reduced, although Tat induced oxidative stress as revealed by the increase in ROS and GSSG and the decrease in manganese superoxide dismutase activity. When *OGG1* expression was knocked down by siRNA, the amount of 8-oxo-dG was increased, suggesting that the Tat-induced reduction of 8-oxo-dG requires *OGG1* gene expression and that the Tat-mediated induction of *OGG1* appears to be independent of Tat pro-oxidant action.

Thus, in addition to its crucial role in viral replication, Tat appears to play a role in maintenance of the genetic integrity of proviral and host cell DNAs. Although various conditions associated with HIV infection and replication are pro-oxidant (12, 13, 57–59), the observed mutations accumulated within the HIV genome have been revealed to be in favor of the G:C to A:T transition (18–22) rather than the G:C to T:A transversion mediated by the oxidative modification. This is in contrast with most of the mutations associated with human cancers, where the G:C to T:A transversion is predominant (28, 29). If induction of *OGG1* were through oxidative stress associated with Tat actions, the level of 8-oxo-dG should have been higher in Tat-expressing cells than in control cells. These findings indicate that Tat-mediated *OGG1* induction is more than a feedback action. Although additional studies are needed, such as the

**FIG. 6.** Mechanism by which Tat induces *OGG1* gene expression: Tat interacts with AP-4 and removes AP-4 from the *OGG1* promoter. A, effect of Tat on AP-4 DNA binding. Nuclear extracts were prepared from Tat/293 and mTat/293 cells, and AP-4 DNA binding was examined by electrophoretic mobility shift assay using AP-4 or mutant AP-4 probes. To verify the AP-4-DNA complex, nuclear extracts were incubated with anti-AP-4 antibody or excess amounts of competitor oligonucleotides (10- or 50-fold). The positions of the specific protein-DNA and supershifted (S.S.) complexes (arrowheads) are indicated. B, interaction between Tat and AP-4 in vivo. Upper panel, cell lysates were prepared, and immune complexes containing Tat or mTat were immunoprecipitated (IP) with anti-AP-4 antibody (decteting Tat). The immunoprecipitates were separated by SDS-PAGE, followed by Western blotting (WB) with anti-AP-4 antibody. One-tenth of each protein lysate used in each reaction was loaded as the input control. Lower panel, Tat/293 and mTat/293 cells were transfected with plasmid expressing Myc-AP-4, and expression of Tat proteins was induced by P0nA (10 μM). The cell lysates were immunoprecipitated with anti-Myc antibody (detecting AP-4), and the immune complex was analyzed for the presence of Tat by Western blotting with anti-FLAG antibody. C, ChIP assay. Upper panel, the *OGG1* promoter region amplified by the primer pairs in ChIP assay is illustrated. Arrows indicate the positions of PCR primers. Lower panels, cell lysates were prepared from Tat/293 and mTat/293 cells that were transfected with plasmid expressing Myc-AP-4 or Myc-LacZ (control) and treated with P0nA (10 μM) for expression of Tat and mTat. Cross-linked chromatin fragments were prepared, and the association of AP-4, LacZ, Tat, and *OGG1* promoter DNA was analyzed by ChIP assay. The recovered DNA was amplified by PCR with promoter-specific primers and analyzed on a 2% agarose gel. DNAs isolated from sonicated cross-linked chromatin fragments were used as inputs. The β-actin promoter DNA was similarly analyzed as a control.
FIG. 7. Reduction in the levels of 8-oxo-dG by Tat. A, electrochemical chromatograms of 8-oxo-dG. The HPLC patterns were traced using an ECD. The 8-oxo-dG peaks (ECD response; shaded areas in the upper panels) are indicated by arrows. The dG peaks (absorption at 290 nm; shaded areas in the lower panels) are also indicated. Cells were treated for the indicated periods of time with PonA (10 μM) to express Tat or mTat. Nuclear DNA samples were prepared and measured for 8-oxo-dG levels. DNA was digested to obtain deoxynucleosides and analyzed with an HPLC-ECD system as described under “Experimental Procedures.” B, levels of 8-oxo-dG in DNA expressing Tat or mTat. The amount of 8-oxo-dG is expressed as the number of 8-oxo-dG residues/10^6 dG residues. The results represent the means ± S.D. from four independent experiments. *, p < 0.005; **, p < 0.001. C, OGG1 knockdown by siRNA. Tat/293 cells were transfected with 100 nM siRNAs directed against various portions of OGG1 (Nos. 1–3) or green fluorescent protein (control) mRNAs. After 72 h of transfection, cells were lysed, and OGG1 protein levels were assessed by Western blotting with anti-OGG1 antibody (upper panel). The blot was stripped and reprobed with anti-α-tubulin antibody (lower panel). D, effects of OGG1 depletion and expression of Tat and AP-4 on the levels of 8-oxo-dG. First bar, control Tat/293 cells (no treatment); second bar, Tat/293 cells transfected with plasmid expressing AP-4; third and fourth bars, Tat/293 cells transfected with siRNA against green fluorescent protein (siRNA control) or OGG1 (No. 1), respectively, and incubated for 72 h; fifth bar, Tat/293 cells transfected with siRNA against OGG1 (No. 1) for 48 h and treated with PonA to induce Tat expression for an additional 24 h. At 72 h post-transfection, nuclear DNA samples were extracted, and the levels of 8-oxo-dG were measured similarly as described for A. The levels of 8-oxo-dG are shown as the fold increase compared with the level of the no-treatment sample (first bar). *, p < 0.05; **, p < 0.01.

Effect of OGG1 mutation on the extent of mutation of viral and cellular genomes during chronic HIV infection, the Tat-mediated induction of OGG1 could be viewed as a regulated “feed-forward” mechanism.

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