Reversal of P-glycoprotein–Mediated Multidrug Resistance in Cancer Cells by the c-Jun NH$_2$-Terminal Kinase

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Abstract

A significant impediment to the success of cancer chemotherapy is multidrug resistance (MDR). A typical form of MDR is attributable to the overexpression of membrane transport proteins, such as P-glycoprotein, resulting in an increased drug efflux. In this study, we show that adenovirus-mediated enhancement of the c-Jun NH$_2$-terminal kinase (JNK) reduces the level of P-glycoprotein in a dose- and time-dependent manner. Protein turnover assay shows that the decrease of P-glycoprotein is independent of its protein stability. Instead, this occurs primarily at the mRNA level, as revealed by reverse transcription-PCR analysis. We find that P-glycoprotein down-regulation requires the catalytic activity of JNK and is mediated by the c-Jun transcription factor, as either pharmacologic inhibition of JNK activity or dominant-negative suppression of c-Jun remarkably abolishes the ability of JNK to down-regulate P-glycoprotein. In addition, electrophoretic mobility shift assay reveals that adenoviral JNK increases the activator protein binding activity of the mdr1 gene in the MDR cells. We further show that the decrease of P-glycoprotein level is associated with a significant increase in intracellular drug accumulation and dramatically enhances the sensitivity of MDR cancer cells to chemotherapeutic agents. Our study provides the first direct evidence that enhancement of the JNK pathway down-regulates P-glycoprotein and reverses P-glycoprotein–mediated MDR in cancer cells. (Cancer Res 2006; 66(1): 445-52)

Introduction

Multidrug resistance (MDR), by which cells resist many structurally and functionally unrelated drugs, is a serious problem in chemotherapeutic management of cancer. The MDR phenotype is most often due to overexpression of drug efflux pumps in the plasma membrane of cancer cells. P-glycoprotein, a 170-kDa transmembrane glycoprotein encoded by the mdr1 gene, is the best characterized drug efflux pump to date and is a member of the ATP-binding cassette transporter family (1–3). A wide range of anticancer drugs has been described to be substrates for P-glycoprotein (e.g., anthracyclines, Vinca alkaloids, and taxanes; ref. 3). Overexpression of P-glycoprotein has been shown to confer MDR in cultured cells and has also been implicated in the clinical drug resistance phenotype. Thus, down-regulation of P-glycoprotein by salvicine, a synthesized diterpenoid quinine (8), was recently reported to play a critical role in the down-regulation of P-glycoprotein activity in cultured cells, the clinical trials of these compounds have not yet been successful, in large part because of their confounded pharmacokinetic interaction with anticancer drugs and their notorious side effects (3). Thus, it is of great importance to develop new compounds or strategies that are capable of circumventing P-glycoprotein-mediated MDR with improved clinical characteristics.

Materials and Methods

Materials. All compounds were purchased from Sigma-Aldrich (St. Louis, MO) and prepared in DM5O. Mouse monoclonal antibody against P-glycoprotein (Calbiochem, La Jolla, CA), rabbit polyclonal antibody against β-actin (Sigma-Aldrich), and horseradish peroxidase–conjugated anti-rabbit and anti-mouse antibodies (Sigma-Aldrich) were obtained from the indicated sources.

Cell culture. The human gastric carcinoma cell line EPG85-257 and human pancreatic carcinoma cell line EPP85-181 and their MDR derivative lines, EPG85-257RDB and EPP85-181RDB, were cultured in Leibowitz-15 medium supplemented with 10% fetal bovine serum and 2 mmol/L l-glutamine at 37°C in a humidified atmosphere with 5% CO$_2$.

Cell proliferation assay. Cells were seeded in 96-well plates at a density of 2 × 10$^4$ per well, and the sulforodamine B assay was then done as described previously (9, 10). The percentage of cell survival as a function of drug concentration was then plotted to determine IC$_{50}$, which stands for the drug concentration needed to prevent cell proliferation by 50%.
Adenovirus preparation and infection. The replication-defective recombinant adenovirus was prepared using the AdenoX expression system (BD Biosciences, San Jose, CA). Briefly, the cDNA of JNK was first cloned into the pShuttle2 vector. The JNK expression cassette was then subcloned into the pAdenoX vector. To produce the adenovirus, the recombinant pAdenoX-JNK plasmid was linearized by digestion with PacI and then transfected into low-passage HEK293 cells as described previously (11). Adenovirus titer was determined with an adenovirus titer kit from BD Biosciences. The multiplicity of infection (MOI) was defined as the ratio of infectious units divided by the number of cells.

Immunocomplex kinase assay. The activity of JNK was measured by using the immunocomplex JNK kinase assay kit (Calbiochem). Briefly, cell lysates were prepared in 20 mmol/L Tris (pH 7.4), 200 mmol/L NaCl, and 1% NP40 with the protease inhibitor cocktail (Roche Applied Science, Indianapolis, IN). The protein concentrations were determined by bicinchoninic acid protein assay (Pierce Biotechnology, Rockford, IL). To immunoprecipitate JNK, cell lysate containing 100 µg of total protein was incubated with a JNK-specific antibody and protein A/G-agarose beads at 4°C overnight. The JNK immunoprecipitates were washed thrice with the cell lysis buffer and then used for the kinase assay, with purified c-Jun as a substrate as described previously (12).

Western blot analysis. Proteins were resolved by SDS-PAGE and transferred onto polyvinylidene difluoride membranes (Millipore, Bedford, MA). The membranes were blocked for 2 hours in TBS containing 0.2% Tween 20 and 5% fat-free dry milk and then incubated first with primary antibodies and then horseradish peroxidase–conjugated secondary antibodies for 2 hours and 1 hour, respectively. Specific proteins were visualized with enhanced chemiluminescence detection reagent according to the manufacturer’s instructions (Pierce Biotechnology). The intensity of protein bands was determined by densitometric analysis with a Lynx video densitometer (Biological Vision).

Semiquantitative reverse transcription-PCR. Total cellular RNA was prepared using the TRizol reagent (Invitrogen, San Diego, CA) following the manufacturer’s instructions. Reverse transcription-PCR (RT-PCR) analysis of mdr1 mRNA expression was done as described previously (13). Equal volumes of RT-PCR reactions were loaded for agarose gel electrophoresis, and the products were quantified by densitometry after ethidium bromide staining.

Drug accumulation. Cells were collected by trypsinization and resuspended in growth medium containing 20 µmol/L daunorubicin or doxorubicin. After incubation at 37°C in 5% CO2 for 1 hour, cells were spun down and washed in PBS. Cells were resuspended in drug-free growth medium and incubated for another 2 hours at 37°C in 5% CO2. The accumulation of drugs in the cells was then analyzed with fluorescence microscopy, and the intracellular fluorescence was quantified with a fluorescence plate reader (Millipore).

Results

Properties of human gastric and pancreatic carcinoma cell lines that display MDR. The MDR cell lines EPG85-257RDB and EPP85-181RDB were derived from EPG85-257 and EPP85-181 cell lines, respectively, by selection in increased concentrations of daunorubicin (14–16). These derivative cell lines were shown to have MDR phenotype by their wide cross-resistance and defects in intracellular drug accumulation. In addition, their MDR phenotype seemed mediated by increased expression of P-glycoprotein but not by MRP-related proteins or BCRP (17, 18). In agreement with the previous studies, cell proliferation assay revealed that the two MDR cell lines exhibited 2,287- and 1,498-fold resistance to daunorubicin, respectively compared with their parental counterparts (Fig. 1A). Similarly, EPG85-257RDB and EPP85-181RDB cell lines were also 3,788- and 2,856-fold more resistant to doxorubicin, respectively, compared with their parental counterparts (Fig. 1A). We examined the level of P-glycoprotein and the level and activity of JNK in the MDR cell lines 7 days after the cells were released to drug-free medium. The MDR cell lines showed robust expression of P-glycoprotein, whereas in the parental cell lines P-glycoprotein was not detectable (Fig. 1B). In addition, both the activity and level of the JNK seemed lower in the MDR cell lines.
Elevated JNK decreases P-glycoprotein levels in MDR cells in a dose- and time-dependent manner. To test a possible role for JNK in regulating P-glycoprotein, we examined the P-glycoprotein level in EPG85-257RDB and EPP85-181RDB cells treated with different MOI adenoviral JNK. Strikingly, adenoviral JNK decreased the P-glycoprotein level in both cell lines in a dose-dependent manner (Fig. 2A and B). For example, in EPG85-257RDB cells, the P-glycoprotein level was reduced by 61.3% from 10.1 × 10^4 to 3.91 × 10^4, arbitrary unit upon treatment with 10 MOI adenoviral JNK for 24 hours (Fig. 2B). A similar effect of adenoviral JNK was seen in EPP85-181RDB cells. In contrast, the adenoviral β-galactosidase control did not have obvious effect on the P-glycoprotein level even at a dose as high as 50 MOI (Fig. 2B).

We also did a time course analysis for the down-regulatory effect of P-glycoprotein level even at a dose as high as 50 MOI (Fig. 2). Additionally, we found that another two P-glycoprotein-overexpressing MDR cell lines, SKOV3R24 and SKOV3R100, which possess 24- and 100-fold resistance respectively, also had lower JNK level and activity than the parental line, SKOV3 (Fig. 1E).

Down-regulation of P-glycoprotein by JNK is independent of P-glycoprotein protein stability. Like several other membrane proteins (19, 20), the level of P-glycoprotein seems regulated by protein stability (21, 22). To investigate whether adenoviral JNK down-regulated P-glycoprotein through this mechanism, we examined P-glycoprotein stability in EPG85-257RDB and EPP85-181RDB cells. Protein turnover assay revealed a half-life of 18.3 hours for P-glycoprotein in EPG85-257RDB cells, which was not significantly altered by adenoviral JNK (Fig. 3A). Similarly, in EPP85-181RDB cells, the half-life of P-glycoprotein was 19.1 hours, and it was only slightly reduced by adenoviral JNK (Fig. 3B). The P-glycoprotein half-life values obtained in these cells were very close to that reported previously (14-17 hours; ref. 23). These results thus suggested that protein stability might play a minor role, if any, in the down-regulation of P-glycoprotein by JNK.

Figure 2. Adenoviral JNK decreases P-glycoprotein (Pgp) protein level in a dose- and time-dependent manner in the MDR cancer cells. A, Western blot analysis of P-glycoprotein and β-actin levels in cells untreated or treated for 24 hours with 5, 10, or 50 MOI adenoviral JNK, or 50 MOI adenoviral β-galactosidase (β-gal) as a control. The level and activity of JNK were also examined to confirm that adenoviral JNK was expressed and functional. B, experiments were done as in (A), and the intensity of P-glycoprotein was quantified by densitometric analysis of the Western blot bands. C, Western blot analysis of P-glycoprotein and β-actin levels in cells treated with 10 MOI adenoviral JNK for 0, 12, 24, 36, or 48 hours. D, experiments were done as in (C), and the intensity of P-glycoprotein was quantified by densitometry. E, adenoviral JNK decreases endogenous P-glycoprotein expression in HCT15 cells. P-glycoprotein and β-actin expression was examined by Western blot analysis in cells untreated or treated with 5, 10, or 50 MOI adenoviral JNK for 24 hours.

JNK down-regulates P-glycoprotein at the mRNA level. To examine whether P-glycoprotein was down-regulated by JNK at the mRNA level, we analyzed mdr1 mRNA expression by semiquantitative RT-PCR. As shown in Fig. 4A and B, 5 and 10 MOI adenoviral JNK decreased mdr1 mRNA expression to similar degrees in both EPG85-257RDB and EPP85-181RDB cells, and 50 MOI adenoviral JNK had a stronger effect, whereas there was no obvious effect for adenoviral JNK treatment. The P-glycoprotein level decreased further upon longer treatment and reached a plateau after 24 hours. To test whether JNK could down-regulate the expression of endogenous P-glycoprotein, we examined the effect of adenoviral JNK in HCT15 cells. As shown in Fig. 2E, the expression of endogenous P-glycoprotein in HCT15 cells was also reduced by JNK in a dose-dependent manner.

The level of P-glycoprotein and the level and activity of JNK in the MDR lines were also examined in the presence of continuous drug exposure and were found similar to those obtained in the absence of continuous drug exposure (Fig. 1D). Additionally, we found that another two P-glycoprotein-overexpressing MDR cell lines, SKOV3R24 and SKOV3R100, which possess 24- and 100-fold resistance respectively, also had lower JNK level and activity than the parental line, SKOV3 (Fig. 1E).
adenoviral β-galactosidase treatment. The dose-effect pattern of adenoviral JNK on mdr1 mRNA was slightly different from that on P-glycoprotein protein, for which 10 and 50 MOI adenoviral JNK had similar effects (Fig. 2A and B). We also found that adenoviral JNK inhibited mdr1 mRNA expression in a time-dependent manner; the mdr1 mRNA kept decreasing over 48 hours of treatment (Fig. 4C and D). This time-effect pattern of adenoviral JNK was also slightly different from that on P-glycoprotein protein, for which P-glycoprotein protein stopped decreasing after 24 hours of adenoviral treatment (Fig. 2C and D). Nevertheless, these data indicated that adenoviral JNK down-regulated P-glycoprotein at the mRNA level.

**JNK activity and c-Jun are required for the down-regulatory effect of JNK on P-glycoprotein.** We then examined whether the

![Figure 3](image-url)

Figure 3. Down-regulation of P-glycoprotein (Pgp) by JNK is independent of P-glycoprotein protein stability. A, decrease of P-glycoprotein over time in EPG85-257RDB cells. Top, Western blot analysis of P-glycoprotein levels. Cells were treated with 10 MOI adenoviral JNK or β-galactosidase (control) for 12 hours and were then treated with the protein synthesis inhibitor cycloheximide (CHX, 20 μg/mL) for 0, 12, 24, 36, or 48 hours. Bottom, quantification of remaining P-glycoprotein at different time points. % Initial P-glycoprotein levels (0 hour of cycloheximide treatment). B, decrease of P-glycoprotein over time in EPP85-181RDB cells. Experiments and quantifications were done as in (A).

![Figure 4](image-url)

Figure 4. Adenoviral JNK decreases P-glycoprotein at the mRNA level. A, RT-PCR analysis of mdr1 and GAPDH mRNA expression levels in cells untreated or treated with 5, 10, or 50 MOI adenoviral JNK, or 50 MOI adenoviral β-galactosidase (β-gal) for 24 hours. B, experiments were done as in (A), and the intensity of the mdr1 RT-PCR product was quantified by densitometry. C, RT-PCR analysis of mdr1 and GAPDH mRNA expression levels in cells treated with 10 MOI adenoviral JNK for 0, 12, 24, 36, or 48 hours. D, experiments were done as in (C), and the intensity of mdr1 RT-PCR product was quantified by densitometry.
indeed increased the AP-1 binding activity of the retic mobility shift assay. Our result revealed that adenoviral JNK enhanced AP-1 binding to the mdr1 promoter, we did electrophoretic mobility shift assay showing that adenoviral JNK increases the AP-1 binding activity of the mdr1 gene in the MDR cells. We treated cells with adenoviral JNK in the presence of SP600125, a small molecule inhibitor of JNK (24). As shown in Fig. 5A, SP600125 not only inhibited the basic activity of endogenous JNK but also inhibited the JNK activity induced by exogenous JNK expression. Furthermore, SP600125 remarkably abolished the down-regulatory effect of JNK on P-glycoprotein (Fig. 5A). Following this observation, we investigated whether the transcription factor c-Jun, the substrate for JNK, played a role for the effect of JNK (Fig. 5B). We treated cells with adenoviral JNK in the presence of dominant-negative c-Jun and then examined the P-glycoprotein level. We found that dominant-negative c-Jun was able to prevent partially JNK-induced down-regulation of P-glycoprotein (Fig. 5B). This result thus indicated a role for c-Jun in mediating the effect of JNK on P-glycoprotein.

The promoter of the mdr1 gene was reported previously to contain a negative binding site of the heterodimeric transcription factor activator protein (AP-1; notably the c-Jun/c-Fos dimer; ref. 25). To test whether JNK down-regulates P-glycoprotein through enhanced AP-1 binding to the mdr1 promoter, we did electrophoretic mobility shift assay. Our result revealed that adenoviral JNK indeed increased the AP-1 binding activity of the mdr1 gene in the MDR cells (Fig. 5C).

JNK-induced down-regulation of P-glycoprotein enhances the intracellular drug accumulation in the MDR cells. We then asked whether the decrease of P-glycoprotein by JNK in the MDR cells could enhance the intracellular accumulation of anticancer drugs. The natural fluorescence of daunorubicin and doxorubicin allowed us to examine their accumulation in cells with fluorescence microscopy. As shown in Fig. 6A, adenoviral JNK resulted in a 3.23-fold increase of daunorubicin in EPG85-257RDB cells and a 4.52-fold increase in EPP85-181RDB cells. Similarly, adenoviral JNK also dramatically enhanced the accumulation of doxorubicin in EPG85-257RDB and EPP85-181RDB cells (Fig. 6B).

Figure 5. JNK activity and c-Jun are required for P-glycoprotein (Pgp) downregulation. A, P-glycoprotein levels in cells treated for 24 hours with 10 MOI adenoviral JNK in the absence or presence of JNK inhibitor SP600125 (SP, 20 μmol/L). P-glycoprotein levels were examined by Western blot analysis and quantified by densitometry. The levels of phosphorylated c-Jun (p-c-Jun) were determined by the immunocomplex kinase assay as a measure of JNK activity, and JNK protein levels were examined by Western blot analysis of the JNK immunoprecipitates. B, P-glycoprotein levels in cells treated for 24 hours with 10 MOI adenoviral JNK in the absence or presence of dominant-negative c-Jun (dn-c-Jun). P-glycoprotein levels were examined by Western blot analysis and quantified by densitometry. The levels of dominant-negative c-Jun and JNK were also examined by Western blot analysis to confirm the expression. C, electrophoretic mobility shift assay showing that adenoviral JNK increases the AP-1 binding activity of the mdr1 gene in the MDR cells.

Adenoviral JNK increases the sensitivity of MDR cells to anticancer drugs. The effects of adenoviral JNK on the P-glycoprotein level and on the accumulation of daunorubicin and doxorubicin suggested that it might be able to sensitize the MDR cells to these drugs. We thus measured the IC50 values of daunorubicin and doxorubicin in EPG85-257RDB and EPP85-181RDB cells treated with adenoviral JNK (Fig. 7). We found that adenoviral JNK decreased the IC50 values of daunorubicin in the MDR cells by >10-fold in these MDR cells, from 7.32 to 0.563 μmol/L in EPG85-257RDB cells and from 11.4 to 0.887 μmol/L in EPP85-181RDB cells (Fig. 7). Similarly, adenoviral JNK also greatly increased the sensitivity of the MDR cells to doxorubicin by >10-fold, from 52.6 to 3.26 μmol/L in EPG85-257RDB cells and from 34.7 to 2.25 μmol/L in EPP85-181RDB cells (Fig. 7). Because JNK activity was shown to mediate apoptosis induced by a wide variety of drugs (12, 26, 27), one could argue that adenoviral JNK might simply sensitize MDR cancer cells to anticancer drugs by lowering the threshold for apoptosis independently of its down-regulatory effect on P-glycoprotein. However, this is very unlikely because adenoviral JNK did not have obvious proapoptotic effect in non-MDR cells, including EPG85-257, EPP85-181, and SKOV3 (Fig. 7C).

Discussion

Chemotherapy is the most effective treatment for patients who suffer from metastatic cancers. The effectiveness of chemotherapy, however, is seriously limited by MDR. Overexpression of P-glycoprotein, an integral membrane protein, represents one of the major mechanisms that contribute to the MDR phenotype. P-glycoprotein functions as a drug efflux pump that actively transports drugs from the inside to the outside of cells and causes
a defect in the intracellular accumulation of drugs necessary for cancer cell killing. Therefore, inhibition of P-glycoprotein transporter function or inhibition of its expression may reverse the MDR phenotype through enhancing intracellular accumulation of anticancer drugs. In the past two decades, there has been a worldwide effort investigating chemical agents for their ability to overcome MDR through interacting with P-glycoprotein and inhibiting its transporter function. These MDR modulators include calcium channel blockers, calmodulin inhibitors, and other classes of compounds. However, none of these compounds has been successful thus far in clinical trials, primarily due to their toxicities at the doses necessary for suppression of P-glycoprotein function and their effects on the pharmacokinetics of anticancer drugs (3).

On the other hand, compounds or strategies capable of decreasing P-glycoprotein expression might be useful in modulating the MDR phenotype and improving chemotherapy. This notion is supported by the data in the present study showing that adenovirus-mediated enhancement of the JNK pathway circumvented P-glycoprotein-mediated MDR in cancer cells through down-regulating P-glycoprotein.

The JNK pathway is known to play a critical role in diverse cellular processes. JNK is activated when cells are exposed to proinflammatory cytokines or environmental stress (e.g., UV and γ-radiation, heat shock, osmotic shock, redox stress, etc.), treated with various anticancer drugs, or undergo growth factor withdrawal. Interestingly, we found that MDR gastric and pancreatic carcinoma cell lines with P-glycoprotein overexpression, EPG85-257RD and EPP85-181RD, respectively, had lower JNK level and activity than their parental counterparts. In addition, SKOV3R24 and SKOV3R100, another two P-glycoprotein-overexpressing MDR cell lines, also

**Figure 6.** JNK-induced downregulation of P-glycoprotein enhances the intracellular drug accumulation in the MDR cells. A, accumulation of daunorubicin in cells treated for 24 hours with 10 MOI adenoviral JNK or β-galactosidase (control). B, accumulation of doxorubicin in cells untreated or treated for 24 hours with 10 MOI adenoviral JNK. Drug accumulation was measured by fluorescence microscopy as described in Materials and Methods. JNK expression was examined by Western blot analysis.

**Figure 7.** Adenoviral JNK increases the sensitivity of the MDR cells to daunorubicin and doxorubicin. A, IC₅₀ values of daunorubicin in cells treated for 24 hours with 10 MOI adenoviral JNK or β-galactosidase (control). B, IC₅₀ values of doxorubicin in cells untreated or treated for 24 hours with 10 MOI adenoviral JNK. JNK expression was examined by Western blot analysis. C, IC₅₀ values of daunorubicin in EPG85-257, EPP85-181 and SKOV3 cells treated for 24 hours with 10 MOI adenoviral JNK or β-galactosidase (control).
displayed lower JNK level and activity than the parental line. It was reported previously that MDR mouse mammary carcinoma cell line FM3A/M also had lower basal and drug-stimulated JNK activities than the parental cell line (6). In addition, reactive oxygen species were shown to down-regulate P-glycoprotein expression accompanied by an increase in JNK activity in multicellular prostate tumor spheroids (7). In another study, salivicine was found to decrease P-glycoprotein expression and increase c-Jun expression; moreover, elevated c-Jun level seemed to be a prerequisite for P-glycoprotein down-regulation by salivicine (8). These studies together suggested a potential negative correlation of JNK activity with cellular levels of drug resistance and that the JNK pathway might be able to down-regulate P-glycoprotein. In this study, we provided the first direct evidence showing that the JNK pathway could indeed reduce the expression of P-glycoprotein in MDR cancer cells.

How might P-glycoprotein expression be down-regulated by elevated JNK? Our data revealed that this might occur primarily at the mdr1 mRNA level and was independent of P-glycoprotein protein stability. Our data also showed that pharmacologic inhibition of JNK activity or dominant-negative inhibition of c-Jun significantly prevented the down-regulatory effect of JNK on P-glycoprotein. These results thus indicated a crucial requirement for JNK activity and c-Jun in mediating JNK-induced down-regulation of P-glycoprotein. It was reported previously that the promoter of the mdr1 gene possesses a negative binding site of AP-1 (c-Jun/c-Fos, etc.; ref. 25). We showed in this study that adenosiviral JNK increased the AP-1 binding activity of the mdr1 gene in the MDR cells. It is therefore very likely that enhanced JNK activity promoted the phosphorylation of c-Jun, which in turn stimulated c-Jun/c-Fos binding to the AP-1 element of the mdr1 gene, thereby leading to the repression of mdr1 mRNA expression and ultimately the repression of P-glycoprotein protein expression. It should be noted, however, that under hypoxia, JNK activity seemed to correlate positively with P-glycoprotein/mdr1 expression (28–30). Therefore, more remains to be learned to generate a clear picture about the molecular basis underlying the regulation of P-glycoprotein/mdr1 expression by JNK. In addition, many other mechanisms have been presented previously for the regulation of P-glycoprotein/mdr1. For example, cross-coupled nuclear factors NF-κB/p65 and c-Fos transcription factors have been reported to negatively correlate with P-glycoprotein/mdr1 expression (28–30). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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