**Salicylic Acid Inhibits UV- and Cis-Pt-induced Human
Immunodeficiency Virus Expression**

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Abstract

Previous studies have shown that exposure of HeLa cells stably transfected with a human immunodeficiency virus-long terminal repeat-chloramphenicol acetyl transferase (HIV-LTR-CAT) construct to many DNA-damaging agents (such as UV light) induces expression from the HIV LTR. By culturing the cells with salicylic acid we demonstrated dose-dependent repression of this UV- or *cis*-Pt-induced HIV expression. While salicylic acid treatment alone decreased viability by up to 50%, equal numbers of viable cells were used for the CAT assays. Repression was evident if salicylic acid was administered 2 h before, at the same time as, or up to 6 h after exposure to the DNA-damaging agent. The kinetics were similar for UV- and for *cis*-Pt-induced HIV expression, and induction was dependent on the UV dose or *cis*-Pt concentration added to the culture. pH changes of the media alone in the absence of salicylic acid did not effect HIV expression. These results suggest a role for the prostaglandins or the cyclooxygenase pathway or both in HIV induction mediated by DNA-damaging agents.

INTRODUCTION

Several years ago, Valerie *et al.* (20) developed a cell line to monitor induction of the human immunodeficiency virus (HIV) promoter through the use of reporter gene expression. HeLa cells stably transfected with an HIV-long terminal repeat-chloramphenicol acetyl transferase (HIV-LTR-CAT) construct have been used by several groups to study the ability of DNA-damaging agents to induce expression from the HIV promoter (17,21,24,38). Similarly, other *in vitro* and *in vivo* studies have demonstrated induction of HIV-LTR expression after exposure to a variety of DNA-damaging and tumor-promoting agents (2,12,16). The mechanism responsible for this induction is unknown. Induction of other genes in response to DNA-damaging agents has been described in many different systems (1,3-6,14,23,25,27); recent studies have postulated involvement of protein kinase C (PKC) (7,26), *p53* (10,11,13), tyrosine kinases (18,19), and other pathways (3,17) in the modulation of gene expression after radiation exposure.

A focus of our laboratory has been on identifying cellular signals involved in the induction of the radiation gene response and in the effects of this induction on cellular function. Our purpose in the current experiment was to study the effects of UV and *cis*-Pt on expression of CAT transcriptionally driven by the HIV-LTR promoter through the use of the prostaglandin inhibitor salicylic acid (or aspirin).

MATERIALS AND METHODS

Cell lines/culture conditions. All experiments were performed by using stably transfected HeLa cells containing a CAT construct driven by the HIV-LTR promoter. The cell line was generously provided by Dr. K. Valerie (Medical College of Virginia) (20).

All cell cultures were maintained in Dulbecco's modified Eagle's medium containing 4500 mg/liter D-glucose, 10% fetal bovine serum, supplemented with penicillin, streptomycin and geneticin. Cultures were incubated at 37 °C under 2.5% CO₂. Cells ranged in confluence from 80–90% at the start of the experiments. They were grown in 100 × 20-mm Petri plates in 10 ml medium. Cell viabilities were performed by trypan blue dye exclusion.

Concentrations of *cis*-Pt (generously provided by Dr. Jeffrey Schwartz, Argonne National Laboratory) and of salicylic acid (2-hydroxybenzoic acid) sodium salt (Sigma) and timeframes for addition of the chemicals and for cell harvests are as described in the text.

Radiation treatments. All irradiations were performed by using 254-nm UV radiation from a General Electric (GE30T8-W) germicidal lamp that was contained in a sterile hood. The irradiations were done 55.6 cm from the source. Before radiation exposures, the media were removed from the Petri plates and centrifuged to remove suspended cells. The plates were washed one time with cold phosphate-

buffered saline (PBS). PBS was discarded, and the cells were irradiated dry without lids at room temperature (dose rate = $2.5 \text{ Jm}^{-2}/\text{sec}^{-1}$). After irradiation, the media were replaced, and the plates were returned to the incubator for a specified time. Dosimetry was performed with a Spectroline DM-254X radiometer. Control cells were left dry with no PBS for 2–10 sec; viabilities were never found to be affected by this absence of liquid medium.

CAT assays. The plates were washed with cold Ca^{2+} - and Mg^{2+} -free PBS, and cells were trypsinized from the plates, washed, and counted. Equal numbers of viable cells from each culture (10^6) were lysed by three freeze-thaw cycles. The cell lysate was then incubated in a reaction mixture containing $40 \text{ } \mu\text{M}$ ^3H -chloramphenicol (31 Ci/mmol) (NEN Research Products) and n-butyryl coenzyme A. CAT was measured by the acetylation of ^3H -labeled chloramphenicol with n-butyryl coenzyme A, which makes the resultant chloramphenicol derivative soluble in xylene. One volume (200 μl) of xylene was then added to 10 ml Eco-Lite scintillation fluid, and the activity, measured by liquid scintillation counting, was directly related to the amount of CAT in the reaction mixture. Results are from a single experiment repeated three times. Variation in absolute cpm was not comparable from one experiment to another because of differences in background and incorporation.

Previous data from our laboratory documented that peak activity of CAT (in cpm) is determined by UV dose or *cis*-Pt concentration and cell number used for the assay (24 and unpublished observations). For all experiments reported here, maximal CAT induction was between 130,000 and 190,000 cpm. Previous work also

substantiated that maximum CAT induction occurs between 15 and 18 h UV exposure (Libertin, Panozzo, Groh, Chang-Liu, Schreck, and Woloschak, submitted).

RESULTS

Effects of salicylic acid on UV-induced HIV expression. Previously published results indicate that HIV-LTR-CAT constructs are inducible in mammalian cells after exposure to different types of DNA-damaging agents, including UV (20,21,24,28). Our current experiments were designed to examine the ability of different agents to modify this induction. Vitamin C and metronidazole did not induce HIV expression when given alone and did not affect UV-mediated HIV-LTR induction (data not shown).

Figure 1 documents the effects of administration of salicylic acid on UV-induced (dose of UV = 25 Jm^{-2}) HIV-LTR expression. A concentration of 10 mg/ml salicylic acid administered at either 3 or 6 h after UV exposure (with cells harvested 24 h after exposure) resulted in repression of the UV response. This occurred even when salicylic acid was administered 12 h after exposure.

Various concentrations (0.2–10 mg/ml) of salicylic acid administered alone demonstrated little effect on HIV expression (Fig. 2).

Additional experiments were performed to examine the effects of varying the concentration of salicylic acid on the UV-induced HIV response (Fig. 3). In these experiments, cells were irradiated with 16 Jm^{-2} and then treated 18 h before harvest (which occurred 24 h after the completion of the radiation exposure) with a range of concentrations (0.2–10 mg/ml) of salicylic acid. These experiments demonstrated that

the salicylic acid-mediated inhibition was dose dependent above a concentration of 1 mg/ml.

By using the 10 mg/ml concentration, we examined the effects of the addition of salicylic acid at varying times after irradiation (Figs. 4 and 5) and demonstrated that inhibition was evident up to 6 h after UV exposure, but was lost sometime between 8 and 12 h after completion of the UV exposure. Similarly, by using the same concentration (10 mg/ml), we examined the effect of prior addition of salicylic acid on HIV expression (Fig. 5) and demonstrated that inhibition occurred if cells were pretreated with salicylic acid up to 2 h before irradiation; experiments when the salicylic acid was washed out of the culture (Fig. 5) suggested that the presence of salicylic acid was important for the inhibitory response to be effective.

Effects of salicylic acid on *cis*-Pt-induced HIV-LTR expression. Previous work in our laboratory also demonstrated that *cis*-Pt is capable of inducing expression of HIV-LTR-CAT in HeLa cells stably transfected with the construct at a peak concentration of 50 mM and at a peak time of 24 h after the completion of the exposure (Panozzo, Panozzo, Ender, Libertin, and Woloschak, in preparation). Our current experiments were further designed to determine the effects of salicylic acid on this *cis*-Pt-mediated induction. Figure 6 demonstrates that salicylic acid is able to inhibit *cis*-Pt induced HIV expression up to 12 h after exposure to the DNA-damaging drug. This response was partially reversible by washing out the salicylic acid 6 h after the treatment. Much like the UV response, the *cis*-Pt induction was inhibitable if the salicylic acid was administered 2 h before, at the time of, or 2 h after *cis*-Pt addition (Fig. 7).

Effects of pH on HIV expression. While these experiments were carried out at pH 7.1, possible microcellular effects of salicylic acid could involve pH changes. To control for this, we examined the effects of pH changes on HIV expression. These experiments examining the effects of pH changes alone or in combination with UV exposure revealed that pH as low as 6.4 had no repressing capacity, and in fact, pH 6.38 exposure alone caused a 1.8-fold induction of HIV expression (data not shown). This suggests that pH changes rendered by salicylic acid in the media (though the media were titrated to neutral when salicylic acid was added to the culture) did not confer the inhibitory response.

Other controls were performed to examine the effects of possible extraneous addition of salicylic acid as a carryover from cell harvest into the CAT assay itself. These experiments demonstrated that the addition of exogenous salicylic acid (0.2, 0.0002 mg/ml) had no effect on the CAT assay itself (data not shown).

DISCUSSION

The results reported here document that salicylic acid, when administered before, immediately after, or up to 6 h after exposure to UV or *cis*-Pt, is able to inhibit induction of HIV-LTR by these DNA-damaging agents. Salicylic acid has been shown to have many effects on mammalian cells, most prominent of which is the inhibition of the synthesis of a variety of prostaglandins and cyclooxygenase pathways (8,22). Our results suggest that the prostaglandins or cyclooxygenase pathway, or

both may be important in the HIV transcriptional response and the overall cellular response to DNA-damaging agents. The intracellular pathways and the actual inducing signals for the DNA damage response have not yet been identified. Nelson and Kastan (13) implicate damaged DNA as the direct intracellular inducing signal, while Stein *et al.* (17) report the possible effects of an intracellular mediator. Working specifically with HIV-1-infected cells, Schreck *et al.* (15) demonstrated that reactive oxygen intermediates (which have been reported as a consequence of DNA damage) activate both NF- κ B and HIV-1 transcription. In actual fact, several pathways activated by DNA-damaging agents and reactive oxygen intermediates may converge to allow for HIV induction. Although prostaglandins or cyclooxygenase pathways may be important, further experiments are required before a more direct relationship between DNA damage gene inductive responses can be linked with these pathways.

Recently, Hughes-Fulford *et al.* (19) showed that exposure of HIV-1 infected T-cells and herpes simplex virus-infected cells with different prostaglandins either inhibits or stimulates viral replication, depending on the conditions. Their results support a role for prostaglandins in the HIV-1 replication/expression machinery, though the level at which the prostaglandins are working is not known. This is consistent with our results documenting requirements for prostaglandins in the HIV transcriptional response.

The timeframe for addition of salicylic acid required to achieve inhibition of HIV expression is during the beginning of the response when prostaglandins are most

likely to be activated, as has been shown in other cell systems (15). The fact that 2-hour pretreatment with the inhibitor creates the same result as 2-hour posttreatment suggests that the first few hours following exposure to the DNA-damaging agent are critical for the induction of HIV, an event that does not peak until 15–24 h after the insult. Addition at later times diminished the level of repression of the UV- or *cis*-Pt-induced HIV response until, at 12 h after exposure, the levels of HIV expression were similar to those of induced cultures in which no salicylic acid was added.

It is interesting that both *cis*-Pt and UV treatments, which result in different types of DNA lesions, induce HIV expression (as do a variety of other DNA-damaging agents) and both are inhibited by the addition of salicylic acid to the culture at similar concentrations and kinetics. The doses of UV and concentrations of *cis*-Pt that induce HIV-LTR expression are those in which over 99% of cells will die as assessed 14 days later in a colony-forming cells assay (Woloschak *et al.*, submitted). Not all DNA-damaging agents induce HIV. Stein *et al.* (17) report no effect of x-rays on HIV expression and Woloschak *et al.* (in revision) have similarly shown that in these HeLa cells gamma rays do not induce HIV expression nor do they act to complement UV-induced HIV expression. The fact that *cis*-Pt and UV-induced HIV expression is inhibitable with salicylic acid suggests that these agents use common elements in their pathways for induction of HIV. Experiments are underway to determine the precise pathways involved in this response.

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FIGURE LEGENDS

Fig. 1. Effects of salicylic acid time of administration on UV-induced HIV expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were untreated (0) or exposed to UV (23 Jm^{-2}) without or with salicylic acid (10 mg/ml) administered 3, 6, or 12 h after irradiation. Cells were harvested 24 h after irradiation.

Fig. 2. Effects of salicylic acid concentration without UV exposure on HIV expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were untreated (0) or exposed to various concentrations (1–10 mg/ml) of salicylic acid administered alone. Cells were harvested 12 h after administration of salicylic acid.

Fig. 3. Effects of salicylic acid concentration on UV-induced HIV expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were exposed to UV (16 Jm^{-2}) with various concentrations (0.2–10 mg/ml) of salicylic acid administered 6 h after UV exposure. Cells were harvested 24 h after irradiation.

Fig. 4. Effects of kinetics of salicylic acid addition on UV-induced HIV expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were exposed to UV (16 Jm^{-2}) without or with salicylic acid (10 mg/ml) administered at various times (3, 6, 12, and 24 h) after UV exposure. Cells were harvested 24 h post-UV exposure.

Fig. 5. Effects of pretreatment with salicylic acid on UV-induced HIV expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were untreated or exposed to UV (16 Jm^{-2}) without or with salicylic acid (10 mg/ml) administered 2 h before (2 h), at the time of (0 h), 4 h after (4 h), 4 h after and washed out 8 h after (4 h/8 h washed out), or 8 h after (8 h) UV exposure. Cells were harvested 24 h after UV exposure.

Fig. 6. Effects of salicylic acid on *cis*-Pt-induced HIV-LTR-CAT expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were untreated (control) or exposed to 50 μM *cis*-Pt without or with salicylic acid (10 mg/ml) added at various times (0 h, 6 h, 12 h, 12 h, 0 h and washed out at 6 h) after *cis*-Pt exposure. Cells were harvested 24 h after addition of *cis*-Pt.

Fig. 7. Effects of salicylic acid on *cis*-Pt-induced HIV expression. HeLa cells stably transfected with an HIV-LTR-CAT construct were exposed to *cis*-Pt (50 μM) at 22 or 24 h. *Cis*-Pt was added 2 h after initiation of the culture. Salicylic acid (10 mg/ml) was added at the same time as (0 h) or 2 h after initiation of the culture, or 2 h after addition of *cis*-Pt. Cells were harvested 24 h after initiation of the culture.

Effects of Salicylate on UV-induced HIV Expression

Figure 1.

Effects of Salicylic on HIV-LTR-CAT Expression

Fig 2

Salicylic Acid given 6 h
prior to harvest;
cells harvested 24 h
post-irradiation

Figure 3.

Figure 4

Effects of Salicylic Acid Pretreatment on UV-induced HIV Expression

Fig 5

Effects of Salicylic Acid on Cis-Pt -
induced HIV-LTR-CAT Expression

Figure 6

Effects of Salicylic Acid on Cis-Pt-induced
HIV Expression

Figure 7