UV Activation of Human Immunodeficiency Virus Gene Expression in Transgenic Mice

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Human immunodeficiency virus (HIV) infection is associated with a clinical latency of as long as 10 years before the development of disease. One explanation for this delay is the requirement of cofactors such as other DNA or RNA viruses, cytokines critical for immune modulation, or environmental UV light. At least in tissue culture studies, these agents are capable of inducing HIV gene expression in cell lines which either harbor the entire viral genome or contain a reporter gene under the control of the viral long terminal repeat regulatory region. The role of these cofactors in terminating clinical latency and inducing disease has been difficult to ascertain because of the lack of an appropriate animal model. We now report that UV light can markedly induce HIV gene expression in transgenic mice carrying both the *cis*-acting (long terminal repeat) and *trans*-acting (the *tat* gene) elements which are essential for viral transactivation and replication in infected cells. Our finding may explain the clinical observations that cutaneous lesions in HIV-infected individuals are often seen in the sunlight exposed areas of the skin, including the face and neck.

The clinical latency associated with human immunodeficiency virus (HIV) can be defined as the long lag time between the initial infection with HIV and the development of clinically apparent disease (18, 20, 26). Because of the potential therapeutic value of prolonging the latent period and preventing the development of active disease after HIV infection, attention has been focused on the underlying mechanisms which hasten the end of clinical latency. In vitro studies have been used to study how cofactors of HIV infection may influence the progression of disease. Such cofactors include coinfecting DNA viruses (17, 25), cytokines critical for immune modulation (10, 27, 45), and environmental UV light (28, 35, 36, 40, 41). These cofactors are capable of inducing HIV expression in cell lines which either harbor HIV and express low but detectable levels of HIV or contain an indicator gene controlled by the HIV long terminal repeat (LTR) regulatory region. Consequently, these cofactors could increase the HIV titer by increasing HIV replication and eventually deplete the target CD4⁺ cells which are infected with HIV. In general, the role of these cofactors in the progression of disease is difficult to determine because of the lack of a good in vivo model with which they can be tested. Approaches used to study latency in individuals include an examination of which tissues and cell types contain HIV (15, 23, 38, 44) and which of those infected cells are actively expressing HIV genes during different stages of clinical disease (4, 8, 12, 13, 24, 31). Even during clinical latency, HIV can be isolated from serum and peripheral blood mononuclear cells (8, 13) and HIV is present in peripheral CD4⁺ T lymphocytes (24, 31). Therefore, HIV gene expression and replication continue during the clinical latent phase, and a true microbiological latency with quiescent HIV may exist in some HIV infected cells but certainly not in all (26).

To better understand how various cofactors influence HIV expression in the clinically latent period, an appropriate

animal model with all of the relevant cell-cell interactions would have clear advantages over many of the available tissue culture systems. We chose to use in our studies transgenic mice containing the HIV type 1 *tat* gene under the control of the HIV type 1 LTR (43). This animal model has the advantage of containing both the *cis*-acting (LTR) and the *trans*-acting (*tat*) element which are necessary for expression and transactivation of HIV genes. The presence of both of these regulatory elements should approximate the requirements of intact HIV for viral gene expression in the infected cell (34) and allow us to analyze their interactions with various cofactors. Given the presence of HIV in the epidermis of the skin (37, 38) and the fact that UV light can activate the HIV LTR in tissue culture cells (28, 35, 36, 40, 41), an obvious concern in HIV-infected individuals would be the finding that UV rays in sunlight can activate HIV in the exposed skin. This activation of HIV may account for the cutaneous lesions seen in HIV-infected individuals in sunlight-exposed areas of the skin (19, 21, 29, 30). Our transgenic mice contain the LTR-*tat* gene in their skin and allow us to test for UV activation of HIV gene expression in vivo.

We have previously demonstrated that the LTR-*tat* transgenic mice selectively express the *tat* gene in the skin (43). We now demonstrate that this expression is localized to the epidermal portion of the skin and can be markedly but transiently induced by UV light at a variety of different wavelengths.

MATERIALS AND METHODS

Derivation of transgenic mice. The generation of transgenic mice containing the LTR-*tat* transgene has been previously described (43). Two independent founder lines designated E10 and F2 were used in these experiments.

Separation of skin into epidermal and dermal portions. Shaved dorsal (back) and ear skin were removed from sacrificed or anesthetized animals, and all underlying fat and muscle were removed. The skin is treated with 0.5 to 1.0%

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trypsin in phosphate-buffered saline without calcium or magnesium for 30 min at 37°C in a 5% CO₂ environment (32). The epidermal portion is then separated from the underlying dermis, and both components are processed for RNA.

Preparation of RNA. RNA was isolated from these tissues by the guanidinium isothiocyanate-CsCl procedure, using a Tekmar tissuemizer probe for tissue disruption. Northern (RNA) blot analysis was performed as previously described (43).

UV light treatment. Both UVC (200 to 290 nm) and UVB (290 to 320 nm) as well as natural sunlight were used to irradiate the animals. A single dose of UVC light of 0.2 mW/cm² for 10 min was provided with a Sylvania germicidal lamp (Thomas Scientific, Swedesboro, N.J.) which had a peak emission of 254 nm. The single dose of UVB irradiation was provided by two FS-40 sunlamps (Westinghouse), which have a peak emission at 313 nm with an irradiance of 0.2 mW/cm² for 1 to 2 h. All dose measurements were performed with a UVX Radiometer (UVP Inc., San Gabriel, Calif.). The mice were also exposed to natural sunlight during October mornings with a surface irradiance of 0.5 to 0.6 mW/cm². Despite rigid temperature control, only 15- and 30-min exposures were tolerated by the mice.

Following anesthesia and removal of dorsal fur with electric clippers, small skin biopsies of dorsal skin and ear were taken immediately before UV irradiation and at the indicated time intervals following UV irradiation.

Histological procedures. Tissue samples of skin were placed in a 10% buffered formalin for 24 h, embedded in paraffin, sectioned, and stained in hematoxylin and eosin.

RESULTS

Epidermal localization of LTR-*tat* expression. We have previously demonstrated that the LTR-*tat* transgenic mice selectively express the *tat* gene in the skin (43). To better understand both how cofactors can affect the expression of the LTR-*tat* gene and to identify the biological effects of *tat* gene expression in these mice, it is important to first determine where *tat* is expressed in the skin. To do so, we separated the skin into the overlying epidermal and underlying dermal portions by treatment with trypsin (32). As shown in the Northern blot assay of poly(A)⁺ RNA (Fig. 1), expression of the LTR-*tat* gene occurs almost exclusively in the epidermal portion of the skin (lane 2), with little or no expression found in the underlying dermal layer (lane 3).

UV light induction of LTR-*tat* expression. To determine whether UV light could induce higher levels of LTR-*tat* expression, the mice were exposed to single doses of both UVC (254 nm) and UVB (290 to 320 nm) light, and both ear and shaved dorsal (back) skin biopsies were taken for analysis. We chose a single dose of UV light that would not cause epidermal or dermal damage as assessed on hematoxylin-and-eosin staining of skin biopsies taken at 24 and 48 h after irradiation. This would avoid the potential complications caused by an inflammatory cell infiltrate and its attendant cytokines which could potentially induce *tat* expression (10, 27, 45).

For UVC irradiation, the nondestructive dose was an exposure of 0.2-mW/cm² irradiance for a time period of no more than 15 min. Compared with the background expression (Fig. 2A, lanes 1 and 3), a 10-min dose of UVC light (0.12 J/cm²) significantly induced *tat* mRNA expression (lanes 2 and 4) taken 8 h after irradiation. Low levels of background *tat* expression were detected since only small amounts of total RNA were used for Northern blot assay;

FIG. 1. Localization of LTR-*tat* gene expression in the skin. Total skin (lane 1), epidermis (lane 2), and dermis (lane 3) from a transgenic mouse were assayed for *tat* expression by Northern blot hybridization analysis of poly(A)⁺ RNA. The corresponding β -actin controls to indicate the relative input amounts of RNA from the various samples are shown in lanes 4 through 6. The top arrowhead indicates the β -actin mRNA, and bottom arrowhead indicates the 0.8-kb *tat* transcript. The minor components migrating behind the 0.8-kb *tat* transcripts are seen only in one transgenic mouse line and most likely were derived from cryptic RNA start sites in the transgene at the site of integration.

this will accommodate the dramatic induction seen upon irradiation. There was no induction of expression in control mice which had biopsies taken at 0 and 8 h but did not receive UVC irradiation.

Since the Tat protein is a potent transactivator of LTR-driven gene expression (34), it is important to study the kinetics of induction by UVC light to determine whether, once activated, expression of the LTR-*tat* gene may be sustained over a long period of time at a high level by the Tat protein. When ear or dorsal skin biopsies were taken at 9 and 21 h following UVC irradiation (Fig. 2B, lanes 2 and 3, respectively), expression was significantly induced at 9 h but has already started to fall back toward the 0-h baseline (lane 1) after 21 h. This observation was highly reproducible in separate experiments in which additional time points were included. The suggestion from this study is that the induction of expression by a single dose of UVC is transient and cannot be maintained by Tat, despite the fact that such transactivation can occur in murine cells (14).

In general, the ozone layer in the atmosphere prevents penetration of UVC irradiation, and individuals on the earth's surface will not be exposed to UVC light unless there is damage to the ozone layer (3, 11). However, UVB irradiation does penetrate the ozone layer and consequently would be a more relevant risk factor for those individuals infected with HIV. We also find that a single dose of UVB irradiation was capable of inducing a significant amount of *tat* expression in both ear and dorsal skin 8 h after treatment (Fig. 3, lanes 2 and 4, respectively) relative to the background expression at 0 hour (lanes 1 and 3, respectively). The single UVB dose consisted of a 1- to 2-h exposure at

FIG. 2. UVC treatment of the LTR-*tat* transgenic mice. (A) Induction of LTR-*tat* gene expression in the skin by UVC (254 nm) irradiation. Small biopsies of shaved dorsal skin and ear skin were taken immediately before UVC treatment (lanes 1 and 3, respectively) and 8 h posttreatment (lanes 2 and 4, respectively). The corresponding β-actin controls are shown in lanes 5 through 8. (B) Kinetics of UVC induction of LTR-*tat* gene expression. Serial dorsal skin biopsies were taken immediately before UVC irradiation (lane 1) and 9 and 21 h postirradiation (lanes 2 and 3, respectively). The corresponding β-actin controls are shown in lanes 4 through 6. Northern blot hybridization analysis was performed on total RNA. The top arrowhead indicates the β-actin mRNA (the band immediately below represents muscle actin RNA from residual muscle tissue in the skin biopsies), and the bottom arrowhead indicates the 0.8-kb *tat* transcript.

0.2-mW/cm² irradiance (0.7 to 1.4 J/cm²), using two sunlamps which have a peak emission at 313 nm. This dose is comparable to those given chronically to mice to induce skin tumors (2, 9) and to study immune functions in the skin (1). By comparison, natural sunlight as measured on the earth's surface has an irradiance of approximately 0.5 to 0.6 mW/cm² at 310 nm. Although natural sunlight is poorly tolerated by mice, we saw induction of *tat* expression in ear skin 8 h following a 30-min exposure (data not shown).

FIG. 3. UVB induction of LTR-*tat* expression in the skin of transgenic mice. Small biopsies of ear and shaved dorsal skin were taken immediately before a 2-h UVB treatment (lanes 1 and 3, respectively) and at 8 h posttreatment (lanes 2 and 4, respectively). The level of induction was about 3-fold in the ear and greater than 10-fold in the back skin. The corresponding β-actin controls are shown in lanes 5 through 8.

DISCUSSION

We have demonstrated that the HIV *tat* gene, under the control of the HIV LTR, is selectively expressed in the epidermal portion of the skin of our transgenic mice and that this expression can be transiently induced to a much higher level by UV light. These observations contrast with those which assayed HIV LTR-directed expression of reporter genes in the absence of the *tat* transactivator (14, 16). Although those studies also noted expression in the epidermal portion of the skin, they also found expression in many other tissues, including thymus, eye, spleen, small intestine, liver, and heart (14, 16). It is likely that this widespread expression represents the basal constitutive activity of the LTR in the absence of the *Tat* transactivator, with detection made possible by sensitive methods such as the chloramphenicol acetyltransferase assay.

Additionally, the use of an indicator gene to assess the ability of UV light to induce LTR-directed expression in the absence of *Tat* (7) is problematic because the magnitude and duration of UV light induction cannot easily be determined. The steady-state level of a mRNA species in the cell is dependent on both its rate of synthesis and its rate of turnover; the stability of the transcript for the indicator gene in the epidermis was not studied (7). Analysis of the *tat* mRNA is, therefore, necessary to accurately determine the extent and half-life of UV light induction.

The mechanisms of activation by UV irradiation in our animal model *in vivo* are likely to be complex. *In vitro* studies of UV induction of the HIV LTR have suggested that changes in chromatin structure may increase transcription by allowing better access of necessary transcriptional factors (28). The *cis*-acting NFκB element in the HIV LTR may also play a role in UV activation of transcription, as suggested in transient transfection assays (36).

To understand the effects of UV light in an *in vivo* animal model, one must also consider the many different potential target cells and how UV light may affect them and interfere

with the complex communications that exist between them. The murine epidermis is predominantly made up of keratinocytes but also contains smaller populations of bone marrow-derived Thy-1⁺ dendritic epidermal cells and Langerhans cells (6, 33, 39). In humans, the latter are known to harbor HIV (37, 38). The effect of UV light on skin in mice has been extensively studied, with particular attention to its effects on the ability of the skin to present antigens and influence the immune system (2, 3, 22). UV light has been found to affect Langerhans cells and cause a decrease in their antigen-presenting ability. The keratinocytes may also respond to UV irradiation with the release of a variety of different cytokines, including interleukin-1, interleukin-6, tumor necrosis factor alpha, and intercellular adhesion molecule 1 (5). These factors may induce a variety of responses in the skin or in other tissues.

The effect of UV light in this transgenic animal model may be to transiently increase the level of *tat* expression in cells in which it is already being expressed at low levels or to activate its expression in cell types in which it is not normally expressed. Our previous findings in these mice suggest that expression of Tat in the epidermal cells may in turn induce the secretion of factors which can affect the proliferation of specific cells in the dermis, leading to the development of Kaposi's sarcoma (43), or in the liver, contributing to the etiology of hepatocellular carcinoma (42). Given that the UV effect on *tat* expression is only transient, it would be of interest to determine whether repeated exposures to UV light will exacerbate the dermal lesions. This study is currently under way.

The implications of our findings for individuals infected with HIV are provocative. There certainly is the suggestion that incident UV irradiation could induce HIV expression in the skin of infected individuals. The single doses of UV light used in these animals are large but attainable in outdoor sunlight. However, the induction of *tat* expression in this model is transient, and repeated exposures to UV light would be required to sustain a high level of Tat protein in the involved cells. This animal model should allow us to determine both the biochemical and functional consequences of UV irradiation on HIV expression.

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