Human T-Lymphotrophic Virus Type 1 p30II Functions as a Transcription Factor and Differentially Modulates CREB-Responsive Promoters

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Human T-lymphotropic virus type 1 (HTLV-1), a complex retrovirus, causes adult T-cell lymphoma/leukemia and is linked to a variety of immune-mediated disorders. The roles of proteins encoded in the pX open reading frame (ORF) II gene region in HTLV-1 replication or in mediating virus-associated diseases remain to be defined. A nucleus-localizing 30-kDa protein, p30II, encoded within pX ORF II has limited homology with the POU family of transcription factors. Recently, we reported that selected mutations in pX ORF II diminish the ability of HTLV-1 to maintain high viral loads in infected rabbits. Herein we have tested the transcriptional ability of p30II in mammalian cells by using yeast Gal4 fusion protein vectors and transfection of luciferase reporter genes driven by CREB-responsive promoters. p30II as a Gal4 DNA-binding domain (DBD) fusion protein transactivates Gal4-driven luciferase reporter gene activity up to 25-fold in 293 and HeLa-tat cells. We confirmed nuclear localization of p30II and demonstrate dose-dependent binding of p30II-Gal4(DBD) to Gal4 DNA-binding sites. The transcriptional activity of p30II-Gal4(DBD) was independent of TATA box flanking sequences, as shown by using two different Gal4 reporter systems. Studies of selected p30II mutants indicated that domains that mediate transcription are restricted to a central core region of the protein between amino acids 62 and 220. Transfection of a p30II-expressing plasmid repressed cellular CRE-driven reporter gene activity, with or without Tax expression. In contrast, p30II at lower concentrations enhanced HTLV-1 long terminal repeat-driven reporter gene activity independent of Tax expression. These data are the first to demonstrate a transcriptional function for p30II and suggest a mechanism by which this nuclear protein may influence HTLV-1 replication or cellular gene expression in vivo.

Human T-lymphotropic virus type 1 (HTLV-1) is a complex retrovirus that encodes typical gag, pol, and env gene products as well as unique regulatory and accessory genes (11). HTLV-1 causes adult T-cell leukemia/lymphoma (ATL) and is etiologically linked to tropical spastic paraparesis/HTLV-associated myelopathy (HAM/TSP), a chronic neurodegenerative disorder (12, 21), as well as a variety of other immune-mediated diseases (10). The role of HTLV-1 in mediating these diseases is not clear but is likely related to the ability of the virus to evoke lymphocyte activation (14). The complex genome of HTLV-1 contains unique regulatory and accessory genes in four open reading frames (ORFs), I to IV, of the pX region. ORFs IV and III of HTLV-1 encode the well-characterized Tax and Rex proteins, respectively. Tax is a 40-kDa nucleolus-localizing phosphoprotein which increases viral transcription from the HTLV-1 long terminal repeat (LTR) as well as many cellular genes involved in host cell proliferation (19). Rex is a 27-kDa nucleolus-localizing phosphoprotein that increases the cytoplasmic accumulation of nonspliced and singly spliced viral RNA (13).

In contrast to the extensive knowledge of Tax and Rex structure and function, little is known about the role of pX ORF I and ORF II in the replication or pathogenesis of HTLV-1. However, emerging evidence supports the expression of pX ORFs I and II both in vitro and in vivo and the importance of these conserved ORFs in the replication of HTLV-1. At least eight alternatively spliced mRNAs are expressed from the 3′ or pX region of HTLV-1 (2). Reverse transcription-PCR assays identified mRNAs from infected cell lines and freshly isolated cells from HTLV-1-infected subjects (17). Cerese et al. (3) reported the detection of the same RNA species from patients with ATL and HAM/TSP using a semiquantitative RNase protection assay. Importantly, cytopotoxic CD8+ T cells from HTLV-1-infected individuals have recently been demonstrated to recognize pX ORF I- and II-derived peptides, indicating that these viral proteins are expressed in vivo (22). Despite evidence for the expression of pX ORF I and ORF II, these viral genes do not appear to be required for viral infectivity, replication, or transformation in typical cell culture systems. In contrast, using an infectious molecular clone of HTLV-1 (7) with selective mutations that ablated the mRNA from ORF I (encoding p12I), we were the first to identify a functional role of pX ORF I in establishment of infection in an animal model (6).

ORF II is spliced to the first tax exon and encodes two proteins, a full-length p30II and an internally initiated p13II. The smaller protein, p13II, is derived from initiation at the first internal methionine codon in ORF II and represents the carboxyl-terminal 87 residues of p30II. The p30II and p13II proteins were initially found to localize to the nucleolus and nucleus, respectively (16), but p13II also localizes to mitochondrial membranes (5). The cellular segregation of ORF II gene products suggests specific roles for these proteins in the regulation of cellular and viral processes.
of HTLV-1 expression or as mediators of virus-cell interactions. The p30H protein contains serine- and threonine-rich regions with distant homology to transcription factors Oct-1 and -2, Pit-1, and POU-M1 (4). We have recently reported that mutations in the ACH/p30H/p13 viral clone which destroy the initiator methionine of the mRNA encoding p13H and insert an artificial termination codon in the mRNA encoding p30H prevent the virus from obtaining normal levels in rabbits (1).

In this study, we have tested the transcriptional ability of p30H in mammalian cells by using a yeast Gal4 fusion protein system and the levels of luciferase reporter gene activity driven by CREB-responsive promoters. Our data indicate that p30H, as a Gal4 fusion protein, significantly transactivates Gal4-driven luciferase reporter gene activity in multiple cell types. Furthermore, we provide data demonstrating that the transcriptional activity of p30H-Gal4 DNA-binding domain (DBD) (DBD) is independent of TATA box flanking sequences by comparing two different Gal4 reporter systems. Mutational studies of p30H indicated that the transactivation domains reside within the central portion of the protein (between amino acids 62 and 220). Interestingly, small amounts of p30H expression transactivated HTLV-1 LTR-driven reporter gene activity, even in the presence of Tax, whereas higher concentrations repressed LTR and CRE-driven reporter gene activity. Our data provide the first evidence to support the transcriptional activity of p30H and suggest an important role for the nuclear protein in HTLV-1 replication and cellular gene expression.

MATERIALS AND METHODS

Cell lines. All cultured cells (293 cells obtained from American Type Culture Collection, no. CRL-1573, and HeLa-tat cells were from the National Institutes of Health AIDS Research and Reference Reagent Program [catalog no. 502]) were grown in 10-cm tissue culture dishes in Dulbecco’s minimal essential medium (DMEM) containing 10% fetal bovine serum and 1% streptomycin and penicillin at 37°C. Cells were split and cultured in six-well plates to 50% confluence 16 h before transfection according to the manufacturer’s protocol (Lipofectamine-Plus; Gibco-BRL).

Gal4-mediated transactivation assay. (i) Reporter plasmids. Plasmid p5XGAL-TATA-Luc, a kind gift of P. Quinn (The Pennsylvania State University, Hershey, Pa.), and p5XGAL-Gal4 DNA-binding domain (DBD) (DBD) were independent of TATA box flanking sequences by comparing two different Gal4 reporter systems. Mutational studies of p30H indicated that the transactivation domains reside within the central portion of the protein (between amino acids 62 and 220). Interestingly, small amounts of p30H expression transactivated HTLV-1 LTR-driven reporter gene activity, even in the presence of Tax, whereas higher concentrations repressed LTR and CRE-driven reporter gene activity. Our data provide the first evidence to support the transcriptional activity of p30H and suggest an important role for the nuclear protein in HTLV-1 replication and cellular gene expression.

(ii) Effector plasmids. The p5XGal4-DBD expression vector was constructed by replacing the CREB-(1-247)-encoding sequence of CREB-Gal4-pCRG4-11 (a kind gift of P. Quinn, The Pennsylvania State University) with the p5XGAL-encoding sequence synthesized by PCR amplification with 5′ primer 5′-ATATGAAATTGACGAGAAGGTCCCGTGTT (TTG-3′) and 3′ primer 3′-AATACTGTTAGAGGTTCCAGG (3′-A). The 5′ EcoRI and 3′ SphI restriction sites (underlined).

(iii) Gal4 DNA-binding sequence using luciferase reporter gene vector (Promega), and then subcloning tandem copies of nase (PEPCK) gene in a luciferase reporter gene plasmid (25). pGL2-TATA-Luc (p30II-Gal4-pCRG4-11, pCMV-p30II-HA, and Gal4-pCRG4-11) were transfection. Luciferase activity and transfection control methods were performed by a yeast Gal4 fusion protein system and the level of luciferase reporter gene activity driven by CREB-responsive promoters. Our data indicate that p30H, as a Gal4 fusion protein, significantly transactivates Gal4-driven luciferase reporter gene activity in multiple cell types. Furthermore, we provide data demonstrating that the transcriptional activity of p30H-Gal4 DNA-binding domain (DBD) (DBD) is independent of TATA box flanking sequences by comparing two different Gal4 reporter systems. Mutational studies of p30H indicated that the transactivation domains reside within the central portion of the protein (between amino acids 62 and 220). Interestingly, small amounts of p30H expression transactivated HTLV-1 LTR-driven reporter gene activity, even in the presence of Tax, whereas higher concentrations repressed LTR and CRE-driven reporter gene activity. Our data provide the first evidence to support the transcriptional activity of p30H and suggest an important role for the nuclear protein in HTLV-1 replication and cellular gene expression.

(iv) Gal4 transcription assay. Luciferase activity and transfection control methods were performed by a yeast Gal4 fusion protein system and the level of luciferase reporter gene activity driven by CREB-responsive promoters. Our data indicate that p30H, as a Gal4 fusion protein, significantly transactivates Gal4-driven luciferase reporter gene activity in multiple cell types. Furthermore, we provide data demonstrating that the transcriptional activity of p30H-Gal4 DNA-binding domain (DBD) (DBD) is independent of TATA box flanking sequences by comparing two different Gal4 reporter systems. Mutational studies of p30H indicated that the transactivation domains reside within the central portion of the protein (between amino acids 62 and 220). Interestingly, small amounts of p30H expression transactivated HTLV-1 LTR-driven reporter gene activity, even in the presence of Tax, whereas higher concentrations repressed LTR and CRE-driven reporter gene activity. Our data provide the first evidence to support the transcriptional activity of p30H and suggest an important role for the nuclear protein in HTLV-1 replication and cellular gene expression.

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HTLV-1 p30II localizes to the nucleus. Nuclear localization or conditional translocation to the nucleus is a characteristic of most proteins that function as a transcription factor. Previous studies have demonstrated by standard immunofluorescence methods that HTLV-1 p30II was localized in the nucleolus of transfected cells and contained two nuclear localization signals (16). Consistent with previous reports, p30II was detected predominantly in the nuclear fraction of our transiently transfected HeLa-tat cells by immunoblot assay (Fig. 1A). We verified these results using an immunofluorescence assay (Fig. 1B). Our results indicate that, following transfection, p30II accumulates in the nucleus. This subcellular localization and the predicted regional homology of p30II with the POU family of transcription factors suggested to us that p30II could play a role in the regulation of transcription.

p30II increases Gal4-driven luciferase reporter gene activity. HTLV-1 p30II has several important structural characteristics of a transcription factor, including nuclear localization sequences, serine/threonine-rich motifs, and regional homology with the transcription factor Oct-1 in DNA-binding regions. While these observations suggest that p30II may serve a role as a transcription factor, the absence of any information about the cis-acting element(s) in viral or cellular promoters that may interact with p30II precludes standard approaches to testing DNA-binding regions as targets of the viral protein. Therefore, to test if p30II could influence transcription, we used a Gal4 system and constructed p30II as a chimeric protein with the DBD of Gal4. The Gal4(DBD) (amino acids 1 to 147) was cloned into the carboxyl-terminal region of full-length p30II (amino acids 1 to 241) to form the p30II-Gal4(DBD) expression vector (p30II-Gal4-pCRG4-11) (Fig. 2A). We initially tested a reporter construct, p5XGT-TATA-Luc, whose promoter contains five copies of the Gal4 DNA-binding site upstream of the TATA box derived from the PEPC-K promoter (−61 to +1) (Fig. 2A). As expected, cotransfection of the parent Gal4-pCRG4-11 vector with p5XGT-TATA-Luc resulted in no significant luciferase reporter gene activity (Fig. 2B). In contrast, in a dose-dependent manner, p30II-Gal4-pCRG4-11 elicited up to an 18-fold mean increase in reporter gene activity (Fig. 2B). The fact that p30II in the absence of Gal4(DBD) did not significantly promote reporter gene activity indicates a requirement for localization of p30II to the Gal4 promoter (Fig. 2B).

To test whether the observed transactivation of reporter gene activity by p30II-Gal4-pCRG4-11 was dependent on specific flanking sequences adjacent to the TATA box region, the p5XGT-TATA-Luc containing the TATA box from the PEPC-K (−61 to +1) gene promoter was compared with pGL2-TATA-Luc; the PEPC-K promoter contains a minimal TATA box derived from the E1b gene promoter of adenovirus. Both luciferase reporter gene activities were significantly increased (up to 18- to 25-fold) by cotransfection with the p30II-Gal4-pCRG4-11 expression vector (Fig. 2C). These data indicate that transactivation of reporter gene activity by p30II is independent of the flanking sequence of the TATA box. We confirmed the transcriptional activity of p30II in a dose-dependent manner using 293 cells (Fig. 2D).

p30II-Gal4(DBD) binds to the Gal4 promoter in a dose-dependent manner. To test if p30II-Gal4(DBD) bound the Gal4 promoter directly, we quantitatively analyzed the promoter-binding activity of p30II-Gal4(DBD) fusion protein in transfected HeLa-tat cells by EMSA. p30II-Gal4(DBD) in nuclear lysates of HeLa-tat cells bound to Gal4-DNA-binding sequences efficiently and in a dose-dependent manner (Fig. 3). Nuclear proteins (50 to 250 ng) from HeLa-tat cells transfected with 10 μg of p30II-Gal4-pCRG4-11 plasmid for 48 h bound to only one site of the double Gal4-DNA-binding probe (site 1), which resulted in a single shifted band (Fig. 3A, lanes 2 to 6, band 1). Higher concentrations of nuclear lysates (300 to 350 ng) containing p30II-Gal4(DBD) elicited an additional band corresponding to binding of a second binding site by p30II-Gal4(DBD) (Fig. 3A, lanes 7 and 8, band 2). When the nuclear proteins were further increased to 400 ng, both Gal4-DNA-binding sites of the probe were occupied, which resulted in a
predominant and slower migrating band 2 (Fig. 3A, lane 9). The addition of Gal4(DBD)-specific antiserum resulted in a supershifted band (Fig. 3A, lane 10, band 3). In addition, when a 10- to 30-fold excess of nonlabeled Gal4-DNA-binding oligonucleotides were added as competitors to the binding reaction, the shifted bands were efficiently attenuated (Fig. 3A, lanes 11 and 12). Figure 3B illustrates the EMSA band shifts. Collectively, these data indicated that the observed shifted probe bands were p30II-Gal4(DBD) specific and provided direct evidence to show the specific interactions between Gal4(DBD)-containing p30II and the promoter of the Gal4 reporter gene.

**Mutation of p30II reveals a central core that mediates transcriptional activity.** In order to determine the structural motifs of p30II that mediated the transcriptional activity in our Gal4 system, a series of six truncated p30II mutants were fused to Gal4(DBD). These mutants of p30II contained progressive deletions in both the amino- and carboxyl-terminal regions of the protein (Fig. 4A). Each of the p30II mutant proteins was expressed at the expected molecular weight, as indicated by immunoblot analysis (Fig. 4B). Equal amounts of wild-type p30II, Gal4(DBD) and each of the mutant proteins were evaluated by cotransfection with our p5XGT-TATA-Luc reporter gene plasmid in HeLa-tat cells. The luciferase activity elicited by p30II-Gal4(DBD) was compared to luciferase activity elicited by each of the six p30II-Gal4(DBD) mutants (Fig. 4C). Luciferase activity elicited by the serially deleted mutants MT-1 through MT-4 was progressively reduced compared to wild-type p30II-Gal4(DBD) (from 75% to less than 10% of wild-type levels). These data indicate that the amino acid sequence from 62 to 220 of p30II is essential for the transcriptional activity observed in our assays. This observation was further confirmed by mutant MT-5, which represents the central amino acid sequence from 62 to 220 of p30II, which retained 85% of the transactivation of wild-type p30II. Mutant MT-6 includes sequences encoding p13II and elicited only 35% of the transcriptional activity of wild-type p30II, suggesting that p13II by itself does not effectively mediate the transcriptional activity. However, p13II sequences, when deleted from the full-length p30II (MT-1), lost approximately 25% of the transcriptional activity of the wild-type protein. These data are consistent with the mitochondrial localization of p13II, imply-
ing that the protein does not affect nuclear transcription events (5).

**p30II differentially influences CRE- and TRE-mediated reporter gene activity.** To test p30II transcriptional activity in the context of the HTLV-1 promoter, we compared the ability of p30II expressed from a pCMV-p30II-HA expression plasmid to mediate CRE- and TRE-mediated reporter gene activity. Because of the known importance of HTLV-1 Tax in the regulation of these promoter elements, we tested each of our reporter gene systems with simultaneous Tax expression in a dose-dependent manner. Cotransfection of pCMV-Tax consistently increased the basal luciferase activity of both reporter gene constructs from 15- to 25-fold (Fig. 5A). The pCMV-p30II-HA plasmid was cotransfected into 293 cells with the CRE- and TRE-luciferase reporter plasmids in the absence and in the presence of Tax (pCMV-Tax). p30II repressed the cellular CRE-driven reporter gene activity in a dose-dependent manner (Fig. 5B) and also reduced the positive transcriptional effects of Tax (Fig. 5C). Interestingly, lower concentrations of the p30II plasmid (<0.1 μg) consistently activated HTLV-1 LTR reporter gene activity, but increased amounts (>0.1 μg) of the plasmid repressed LTR reporter gene activity (Fig. 5B). Tax expression only modestly influenced this differential pattern of p30II effects on LTR-mediated transcription, and the positive effect of lower concentrations of p30II in LTR-mediated reporter gene activity were additive to typical Tax effects (Fig. 5C). Cotransfection of pCMV-p30II-HA had no effect on expression of pRSV-β-gal (data not shown). These data suggest that low concentrations of p30II have the potential to differentially interfere with the transcription of CRE-driven gene activity while promoting LTR-mediated transcription.

**DISCUSSION**

Our data are the first to demonstrate the functional role of p30II in modulating transcription. Using a yeast Gal4 fusion protein system and transfection of luciferase reporter genes driven by CREB-responsive promoters, we provide evidence to support the ability of p30II to serve as a transcription factor in mammalian cells. Transcriptional activity of the nucleus-localizing p30II-Gal4(DBD) was independent of TATA box flanking sequences, and selected mutant proteins indicate that the transactivation domains of p30II are localized between amino acids 62 and 220. Furthermore, we demonstrated that p30II repressed cellular CRE-driven reporter gene activity, with or without Tax expression, while small amounts of p30II enhanced HTLV-1 LTR-driven reporter gene activity, even in the presence of Tax. Higher concentrations of the viral protein repressed LTR-driven reporter gene activity. Collectively, our data have important implications for the role of p30II in the replication of HTLV-1 and suggest a mechanism by which this nuclear protein may differentially influence HTLV-1 replication or cellular gene expression in vivo.

A growing body of evidence indicates the importance of HTLV-1 pX ORFs I and II in the replication of the virus in vivo. The exact function of the proteins encoded by HTLV-1 ORF II, p30II and p13II, remains elusive. Selective mutations of the infectious ACH clone designed to eliminate p30II and p13II expression do not affect in vitro viral infectivity of HTLV-1 in human peripheral blood mononuclear cells or alter the Gag and Env composition of virus particles or influence Tax function in transfected cell lines (26). However, pX ORF II is highly conserved by the virus. We have recently reported that selected mutations which prevent the expression of full-length p30II and eliminate the start codon for p13II dramati-
cally influence the ability of the proviral clone ACH to maintain proviral loads in infected rabbits (1). Furthermore, Pique et al. (22) have recently reported that cytotoxic CD8\(^+\) T cells from HTLV-1-infected individuals recognize pX ORF I- and II-derived peptides, indicating that these viral proteins are expressed in vivo.

HTLV-1 p30\(^\text{II}\) (also referred to as Tof) contains several important features of many transcription factors. The protein contains a region rich in serine and threonine residues, which are conserved in the transcriptionally important domains of several octamer-binding transcription factors such as Oct-1, Oct-2, and Pit-1. In addition, p30\(^\text{II}\) has nuclear localization signal sequences. These features imply that p30\(^\text{II}\) functions as a transcription factor in HTLV-1-infected cells. Our data suggest that the enhancement of Gal4 reporter gene activity by p30\(^\text{II}\)-Gal4(DBD) specifically results from the interactions between p30\(^\text{II}\) and the transcription complex bound to or associated with the transcription start site. To further define the molecular mechanism of p30\(^\text{II}\)-mediated transactivation, it will be important to identify binding proteins for p30\(^\text{II}\) among the transcription machinery complex.

The results from our p30\(^\text{II}\) mutant studies indicated that the
transactivation motif of p30II was localized in the middle region of the protein (residues 62 to 220). This core region includes the defined nuclear localization signal and serine/threonine-rich regions (4). We found that p30II-Gal4(DBD) mutants with progressive deletions in the C-terminal sequences of p30II (from MT-1 to MT-4) correspondingly lost their ability to mediate transcription. MT-4, representing only the first 62 amino acids of the N terminus, lost almost all of its ability to mediate transcription. MT-5 (62 to 220), which retained the ability to promote reporter gene activity nearly as efficiently as wild-type p30II despite the fact it lacks N-terminal (1 to 62) and C-terminal (220 to 241) sequences. MT-6 (retaining sequences corresponding to p13II) lost as much as 75% of the transactivation of reporter gene activity, suggesting that p13II serves a different role in the viral life cycle (5). Further studies using site-directed mutations are needed to define the particular amino acid residues of p30II that serve as the transactivation domain of the protein.

Our data showing that p30II differentially influences CRE- and TRE-driven reporter gene activity are not without precedence. Similarly, the regulation of the immediate-early (IE) gene promoter of herpes simplex virus type 1 (HSV-1) is dependent on the interplay between cellular and viral transcription factors. VP16, a potent transcription factor from HSV-1, binds the host cell protein HCF, which allows the viral protein to form a stable complex with Oct-1 (29). The IE gene promoter contains an Oct-1-like motif (TAATGARAT) that is critical for IE gene expression. Cellular octamer-binding proteins can mediate the inhibition of IE promoters. The TAATGARAT motif (where R is a purine) has been demonstrated to cause both positive and negative effects, depending on the context of these cellular transcription factors and VP16 (27). As a result, these motifs have been postulated to mediate active transcription of HSV-1 during lytic cycles of replication but silence the IE genes during HSV-1 latency by serving as a target for inhibitory octamer-binding proteins. HTLV-1 p30II may modulate transcription by similar mechanisms. Further studies are in progress to identify the DNA-binding sites or cellular proteins that interact with p30II.

Our data also demonstrated that small amounts of p30II could transactivate HTLV-1 LTR-driven reporter gene activity, whereas increasing concentrations of p30II repressed LTR reporter gene activity. The positive effect of lower concentrations of p30II in LTR-mediated reporter gene activity was additive to the influence of Tax, which only modestly altered the differential pattern of p30II effects on LTR-mediated transcription. A previous report suggested that expression of p30II

FIG. 5. p30II differentially modulates CRE- and TRE-mediated transcription. (A) Luciferase activity of 0.3 μg of α-CRE-luciferase reporter plasmid (solid triangles) or 0.3 μg of pLTR-luciferase reporter plasmid (open circles) and 0 to 1.0 μg of pCMV-p30II HA. The lower panel demonstrates parallel transfections but with 30 ng of pCMV-Tax as well. Results are expressed as arbitrary light units (ALU) to indicate basal activity (without pCMV-p30II HA) and activity following transfection of plasmids. (B) 293 cells transiently cotransfected with 0.3 μg of α-CRE-luciferase reporter plasmid (hatched bars) or 0.3 μg of pLTR-luciferase reporter plasmid (dotted bars) and 0 to 1.0 μg of pCMV-p30II HA. (C) Same transfections as in panel A but also concurrently transfected with 30 ng of pCMV-Tax. Cotransfection of pCMV-p30II-HA had no effect on expression of pRSV-br-gal, used as a transfection control. Results are expressed as mean percent change in arbitrary light units (ALU) ± SD in luciferase activity for four independent trials.
had no positive influence on LTR-Tax reporter gene activity (4). However, this study did not report the concentrations of expression plasmids used to monitor LTR-mediated reporter gene activity or whether p30H was tested in a dose-dependent manner. Our data indicate that the transcriptional effects of p30H on LTR reporter gene activity are concentration dependent. In context to the infected cell, in which small amounts of p30H are likely to be expressed, this viral protein may successfully promote viral transcription while suppressing basal CRE-mediated gene expression.

In summary, this report provides the first evidence that p30H mediates transcriptional activity. We believe that p30H functions in infected cells as either a transcriptional activator or repressor, depending on the cis-acting sequence of the promoter and p30H expression levels. Further studies are required to identify DNA or protein targets that form functional partners with p30H before the role of the viral protein is delineated in context to the replication of HTLV-I or in mediating the pathogenesis of virus-associated diseases.

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