Human T-cell Lymphotropic Virus Type 1 Tax Inhibits Transforming Growth Factor-β Signaling by Blocking the Association of Smad Proteins with Smad-binding Element*

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The human T-cell lymphotropic virus type 1 (HTLV-1) oncoprotein Tax is implicated in various clinical manifestations associated with infection by HTLV-1, including an aggressive and fatal T-cell malignancy. Because many human HTLV-1-infected T-cell lines are resistant to the growth inhibitory activity of transforming growth factor-β (TGF-β), we examined the possibility that the HTLV-1-Tax oncoprotein regulates TGF-β signaling. We show that Tax significantly decreases transcriptional activity and growth inhibition in response to TGF-β. Tax inhibits TGF-β-induced plasminogen activator inhibitor-1 expression and Smad2 phosphorylation. Competitive interaction studies show that Tax inhibits TGF-β signaling, in part, by disrupting the interaction of the Smads with the transcriptional co-activator p300. Tax directly interacts with Smad2, Smad3, and Smad4; the Smad MH2 domain binds to Tax. Furthermore, Tax inhibits Smad3-Smad4 complex formation and its DNA binding. These results suggest that suppression of Smad-mediated signaling by Tax may contribute to HTLV-1-associated leukemogenesis.

Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that causes both adult T-cell leukemia (ATL) and the degenerative neuromuscular disease tropical spastic paraparesis, or HTLV-1-associated myelopathy (1, 2). The mechanism of HTLV-1 pathogenesis is still unclear, but it has been postulated that a 40-kDa Tax protein, which HTLV-1 pro-viral DNA encodes, is involved in the hyper-proliferation and transformation of T-cells in ATL. The viral Tax protein not only regulates HTLV-1 gene expression but also stimulates the degenerative neuromuscular disease tropical spastic paraparesis, or HTLV-1-associated myelopathy (1, 2). The mechanism of HTLV-1 pathogenesis is still unclear, but it has been postulated that a 40-kDa Tax protein, which HTLV-1 pro-viral DNA encodes, is involved in the hyper-proliferation and transformation of T-cells in ATL. The viral Tax protein not only regulates HTLV-1 gene expression but also stimulates the growth and transformation of T-cells in ATL. This viral Tax protein only regulates HTLV-1 gene expression but also stimulates the transcription of several cellular genes including activating transcription factors/CRE-binding proteins (CREB) (3), NF-E2 (4–6), p62SP1 (7, 8), Ets1 (9), NF-Y (10), and Sp1 (11). In addition, Tax binds to the basal transcription factors TFIIA (12) and TFIIB, and to TFIID through the TATA-binding protein (13) and TATA-binding-protein-associated factor TAFII (14). Moreover, Tax interacts with CREB-binding protein (CBP) (15, 16), a cofactor facilitating transcriptional activation by CREB. Through these interactions, Tax enhances the expression of a variety of target genes related to cellular activation and growth. These include genes for transforming growth factor-β1 (TGF-β1), interleukin-2, interleukin-6, granulocyte-macrophage colony-stimulating factor, Fra-1, c-Myc, c-Fos, and c-Jun (17–24). Aberrant expression of these proteins may be involved in the dysregulated proliferation of HTLV-1-infected cells.

Tax also induces cell cycle progression through direct interaction with cell cycle regulators. Tax binds and inactivates p16INK4a, a negative regulatory molecule of the cell cycle (25). Tax may also directly associate with cyclin D, which is important in cell cycle transition from the G1 to S phase (26). Recent studies suggest that the mechanism of Tax-mediated cellular transformation is a failure to repair DNA damage. As a consequence, Tax-expressing cells accumulate aneuploidogenic and clastogenic lesions which are postulated to lead to a transformed phenotype (27, 28).

TGF-β inhibits the growth of most epithelial and lymphoid cells, and this negative regulation of cellular proliferation by TGF-β has been shown to constitute a tumor suppressor pathway (29, 30). Smad2 and Smad3 have been identified as direct downstream mediators of TGF-β signaling (31). Receptor-mediated phosphorylation of these Smads induces their association with the shared partner Smad4 followed by translocation into the nucleus where these complexes activate transcription of specific genes (32, 33). Smad proteins contain a conserved amino-terminal domain (MH1) that binds DNA (34), and a conserved carboxy-terminal domain (MH2) that binds receptors, partner Smads, and transcriptional coactivators (35). These two domains are separated by a more divergent linker region.

A previous report demonstrated that HTLV-1-infected T-cell lines become resistant to TGF-β growth inhibitory activity (2). We hypothesized that this TGF-β resistance results from the HTLV-1 Tax protein, and we examined whether Tax alters TGF-β signaling. In this study, we demonstrate that Tax inhibits the transcriptional activation and growth inhibition responses to TGF-β. Tax inhibits TGF-β signaling, in part, by competitive interactions with both Smad proteins and p300. We also show that Tax binds to Smad2, Smad3, and Smad4 directly. Furthermore, we demonstrate that Tax prevents binding of the Smad complex to its target sequence, and thereafter inhibits TGF-β signal transduction. These results suggest that the inhibition of TGF-β signaling by Tax may lead to the HTLV-1-associated leukemogenesis.

MATERIALS AND METHODS

Constructs—FLAG-tagged Smad2, -3, and -4 deletion constructs were generated by polymerase chain reaction using a proofreading polymerase and subcloned EF-FLAG vector. All polymerase chain reaction-generated products were sequenced using the dideoxynucleotide method.
RESULTS

Transcriptional Repression of a TGF-β-responsive Gene by Tax—To examine the role of Tax in TGF-β-induced transcriptional activation, we co-transfected HepG2 cells with a Tax expression construct and either the TGF-β-responsive 3TP-lux reporter construct or SBE4-luc, which contains four SBE (Smad-binding element) sites in tandem (39). Introduction of Tax repressed the TGF-β-dependent activities of these reporter gene constructs (Fig. 1, A and B) suggesting that Tax represses TGF-β-induced transactivation. The repression of the SBE4-luc reporter activity by Tax suggests that it may directly inhibit the transcriptional activation of Smad complexes. To confirm that Tax is directly involved in Smad-mediated transcriptional activation, we used a heterologous reporter assay in which the Gal4 DNA-binding domain was fused to various Smad proteins. Gal4-Smad2, Gal4-Smad3, or Gal4-Smad4 expression constructs were cotransfected with a luciferase reporter construct (G5E1b-lux), which contained five Gal4-binding sites upstream of the AdE1b TATA box. As expected, TGF-β treatment did not induce transcription by the minimal Gal4-DNA binding domain, and Tax did not have any effect on its transcription. However, cotransfection of a Tax expression vector with Gal4-Smad2, Gal4-Smad3, or Gal4-Smad4 decreased the TGF-β-dependent activation of these constructs (Fig. 1C), demonstrating that Tax can directly diminish Smad-mediated transcriptional activation.

To examine whether Tax renders resistance to the TGF-β growth inhibitory activity, we generated Mv1Lu mink lung epithelial cells stably expressing Tax. TGF-β inhibited the proliferation of control Mv1Lu cell, whereas overexpression of Tax abrogated TGF-β growth inhibitory activity (Fig. 2A). We also examined the inhibitory effect of Tax on the TGF-β-induced induction of the endogenous target gene. An asynchronous population of either control CV-1 or Tax-expressing CV-1 cells was incubated with the 3TP-lux reporter plasmid and stored at −80 °C. The extract (30 μg) was incubated with the oligonucleotide probe (41) labeled with [3H] (2 × 10^6 cpm) in 20 μl of reaction buffer at room temperature for 20 min, and the reaction mixture was analyzed by electrophoresis on a 4% nondenaturing polyacrylamide gel and run in 0.5× Tris borate-EDTA buffer. After electrophoresis the gel was dried and autoradiographed.

Competition between Tax and Smad for Binding to p300—To address the mechanism whereby Tax suppresses the transcriptional activation of the TGF-β signal transduction pathway, cells were co-transfected with Tax and an increasing dose of either p300 or p300/CBP-associated factor (p300/PCAF) (Fig. 3A). A previous study has demonstrated that Tax inhibits the ability of the Smads to mediate TGF-β-induced transcriptional activation by interfering with the recruitment of CBP/p300 (43). We confirmed this observation as well. As shown in Fig. 3A, Tax inhibited the TGF-β-induced transcriptional activity, but p300 restored the suppression of the TGF-β-induced transcriptional activation by Tax in a dose-dependent manner. PCAF, however, failed to restore the suppressed activity. Tax also suppressed, in a dose-dependent manner, the potentiation of the TGF-β transcriptional activity by p300 (Fig. 3B). These results suggest that Tax may block the interaction between the Smads and p300. To confirm this hypothesis, we assessed the interac-
tion between transfected Smad2 and endogenous p300 in HepG2 cells in the presence or absence of Tax. Immunoprecipitation of endogenous p300, followed by Western blotting with FLAG antibody to detect Smad2, showed that overexpression of Tax interferes with the interaction of p300 with Smad2. Increasing the amount of transfected Smad2 overcame the Tax-mediated inhibition and restored the Smad2/p300 association (Fig. 3C). These data suggest that Tax inhibits Smad signaling by competing with Smad2 for binding to p300.

**Tax Interacts with Smads**—To examine the possibility that Tax interacts directly with Smad proteins, we used HepG2 cells transfected with a Tax expression vector and FLAG/Myc-tagged Smad expression constructs. There was a ligand-independent interaction between Tax and Smad2, Smad3, or Smad4 (Fig. 4, A–C). Immunoprecipitation assays were also performed using SW480 cell extracts. We had the same results as in HepG2 cells (data not shown). The interaction between these Smad proteins and Tax was also studied by GST pull-down assays *in vitro* using 35S-labeled Smad2, -3, and -4 proteins. Tax interacted with 35S-labeled Smad2, -3, or -4 (Fig. 3D). These results demonstrated that Tax binds to Smad2, -3, or -4 directly.

To demonstrate that Tax interacts with Smad2, -3, and -4 *in vivo*, C81 cells, an HTLV-1-transformed T-cell line that constitutively expresses Tax, were used (44). Whole cell extracts were prepared from C81 cells and from Jurkat cells for control. Expression of endogenous Smad2, -3, and -4 was confirmed by Western blot analysis using rabbit polyclonal antibodies against these proteins (Fig. 4). Tax was only detected in C81 cells (Fig. 5A, the bottom panel of lane 2). Total cell extracts were prepared from Jurkat and C81 cells and immunoprecipitated with anti-Tax antibody or Smad3 antibody. The resulting
Western blots demonstrate that Tax was specifically co-immunoprecipitated with endogenous Smad2, -3, or -4 (Fig. 5B).

**Tax Interacts with the MH2 Domain of Smads—**Immunoprecipitation assays were performed using various FLAG-tagged Smad2, Smad3, or Smad4 expression constructs along with a full-length Tax to determine the domain of Smad2, -3, or -4 interacting with Tax. Tax was found to associate with the carboxyl-terminal MH2 domain of Smad2, -3, or -4, but not with the amino-terminal MH1 or middle linker domain of this molecule (Fig. 6, B, D, and F), demonstrating that the MH2 domain contained the Tax interaction domain.

Because Tax interacts with the MH2 domains of the Smads, which are the R-Smad/Smad4 interaction domains, we examined whether Tax inhibits this complex formation. The Myc-tagged Smad4 expression construct was co-transfected with the FLAG-tagged Smad3 expression construct to determine whether the Tax expression construct interferes with the interaction of Smad3 and Smad4. After 24 h of transfection, cells were incubated in the presence or absence of TGF-β1 for 30 min and whole cell extracts were prepared. To investigate Smad3/Smad4 complex formation, total cell extracts were immunoprecipitated with anti-Myc antibody and FLAG-Smad3 bound to Myc-Smad4 was examined using anti-FLAG antibody by Western blot analysis. As shown in Fig. 7, Tax expression markedly decreased the level of Smad3 bound to Smad4, demonstrating that Tax inhibits R-Smad3/Smad4 complex formation.

**Tax Mutant M47 Failed to Repress TGF-β-induced Transcription because of Defective Interaction with Smad3—**To confirm the mechanism of Tax blocking on TGF-β signaling, we examined the effect of Tax mutants M22 and M47 on TGF-β-induced transcription. M22 (T130A,L131S) is a mutant that is partially defective in dimerization (45, 46). In contrast, M47 (L319R,L329S) is a COOH-terminal mutant that retains the ability to form dimers and bind CREB (45, 46). In the luciferase assays using 3TP-Lux, a TGF-β-responsive reporter plasmid, both wild-type Tax and M22 were able to significantly repress the TGF-β-dependent activities of this reporter gene construct. However, Tax mutant M47 failed to repress TGF-β-induced transactivation (Fig. 8A). Using these Tax mutant constructs together with a wild-type Tax, we performed immunoprecipitation assays with anti-FLAG antibody for Smad3. As shown in Fig. 8B, wild-type Tax and M22 showed interaction with Smad3, however, the ability of M47 to interact with Smad3 was markedly decreased (Fig. 8B). This result suggests that M47 cannot repress TGF-β transcription activity because of its inability to interact with Smad3.

**Tax Inhibits the Formation of the Smad3-containing Complex—**Using M22 and M47 Tax mutants together with a wild-type Tax, we performed the CAGA binding assay (41) after transient transfection into HepG2 cells. In Fig. 9A, TGF-β treatment showed Smad3 binding to the CAGA element (upper panel, lane 2), and this binding is significantly diminished in the wild-type Tax-transfected HepG2 cells (lane 3). However, Tax mutant M47 failed to block this binding (Fig. 9A, lane 4). In contrast, M22 showed the inhibitory activity on this binding as much as wild-type Tax (Fig. 9A, lane 5).

To examine whether Tax inhibits the formation of the Smad-containing complex, we also performed a gel shift assay using an oligonucleotide encompassing a TGF-β-responsive element in the plasminogen activator inhibitor-1 promoter. HTLV-1 Tax Represses Smad-mediated TGF-β Signaling.

**Fig. 2.** Tax block the TGF-β growth activity. A, Tax-expressing Mv1Lu cells and control cells were treated with varying concentrations of TGF-β1 as indicated. After 22 h of TGF-β1 treatment for the cells, the cells were pulsed with [3H]thymidine and harvested 2 h later. The experiments were repeated three times. All values represent the averages of the three determinations mean ± 1 S.D. Expression of Tax protein was analyzed by Western blots using anti-Tax antibody in Tax-expressing Mv1Lu cells (B) and CV-1 monkey kidney cells (C). D, effect of Tax on the level of β21 protein induced by TGF-β. Asynchronously growing CV-1-neo and CV-1-Tax cells were incubated in the presence or absence of TGF-β1 for 24 h. p21 protein levels on the whole cell lysate were examined by Western blot analysis. β-Actin protein levels were examined for the loading control. E, Western blot analysis of Smad2 activation in CV-1-neo and CV-1-Tax cells. After treatment for 30 min with TGF-β1 (5 ng/ml), a band of 58 kDa representing phosphorylated Smad2 (Smad2P) was detected in cell extracts by immunoblotting using rabbit anti-Smad2P antibody. TGF-β1 induced phosphorylation of Smad2 in CV-1-neo cells, but the level of Smad2 phosphorylation was markedly decreased in CV-1-Tax cells.
Previous studies have shown that co-transfection of a constitutively active TGF-β type 1 receptor (TβRI-T204D) together with Smad3 and Smad4 generates a Smad-containing complex visualized in a gel-shift assay and this complex can be supershifted with either Smad3 or Smad4 antibodies (31). Nuclear extracts were prepared from the CV-1-neo and CV-1-Tax cells after TGF-β1 treatment. TGF-β1 treatment markedly increased the formation of the Smad-containing complex in CV-1-neo cells, whereas expression of Tax in CV-1-Tax cells prevented the formation of the Smad-containing complex (Fig. 9B).

These data strongly indicate a direct inhibitory role of Tax on the formation of the Smad-containing complex.

**DISCUSSION**

The pathogenesis of ATL is still not understood, but it has been postulated that the viral Tax protein is involved in the proliferation and transformation of T cells in ATL. Tax is known to modulate cellular proliferative responses through two broad mechanisms. First, Tax directly targets specific transcriptional regulators including E2F, CREB, NFκB, SRF, 1xb, and CBP/P300. The regulation of E2F is a key target for oncoretroviruses. Binding of pRB and the other pocket proteins to viral proteins, such as adenovirus E1A, simian virus large T antigen, and papillomavirus E7, leads to a stimulation of E2F-dependent transcription. The induction of the E2F DNA binding activity in HTLV-1-infected T-cell lines and in leukemic cells obtained from ATL patients suggests that the activation of E2F-dependent transcription by HTLV-1 could be involved in the proliferative response during HTLV-1 infection (44). Second, in addition to transcriptional regulation, Tax modifies cell cycle regulators, primarily by affecting inhibitors of cyclin-dependent kinases. Tax binds to and inactivates the p16INK4a protein, which belongs to the INK four family of cyclin-dependent kinase inhibitors (25), thus resulting in the activation of cyclin-dependent kinase 4. This effect of Tax relieves cells from p16INK4a-induced growth arrest and may also contribute to the cellular immortalization and transformation induced by HTLV-1 infection.

Our studies have suggested yet another mechanism by which
Tax may promote cellular proliferation and transformation. Hollsberg et al. (47) have previously shown that HTLV-1-infected T-cell lines become resistant to TGF-β-induced growth arrest. We suspected that the source of this TGF-β resistance resides in the HTLV-1 Tax protein, and that, given the numerous studies that have documented that loss of TGF-β signaling promotes tumor formation, this TGF-β resistance may provide an important means by which these cells become oncogenic.

Therefore, to investigate the carcinogenic mechanism of HTLV-1, we explored the influence of Tax on TGF-β signaling. 3TP-Lux and SBE reporter assays, which test the integrity of the entire TGF-β signaling pathway, were substantially inhibited by Tax, clearly indicating that Tax affects some portion of the TGF-β signal transduction cascade. We next localized the point within the pathway at which this blockade occurs by demonstrating that Tax associates with Smad proteins, di-
During the preparation of this manuscript, Mori et al. (43) reported that Tax inhibits TGF-β signaling, but does not bind to Smad proteins, a conclusion that is contrary to the results of the present study. The precise reason for this discrepancy is not clear at the present time. Interaction between Tax and Smad proteins may be cell-type specific. One potential argument is that the observed interaction between Tax and Smad in HepG2 cells is an artifact of overexpression of these proteins. However, the results obtained from C81 cells, a cell line that was established from a patient with HTLV-1-induced acute T-cell leukemia (44), unequivocally demonstrate that Tax binds to Smads.
proteins (Fig. 5). We have also shown the direct interaction between Smads and Tax by in vitro GST pull-down assays using 35S-labeled Smad2, -3, and -4 proteins (Fig. 4D). To confirm our findings, we examined the effect of Tax mutants, M22 and M47, on TGF-β-induced transcription. In luciferase assays using 3TP-lux, M47 failed to show inhibitory activity on the TGF-β-induced transcription. In contrast, M22 showed significant inhibition (Fig. 8A). This result confirms the finding by proteins (Fig. 5). We have also shown the direct interaction between Smads and Tax by in vitro GST pull-down assays using 35S-labeled Smad2, -3, and -4 proteins (Fig. 4D). To confirm our findings, we examined the effect of Tax mutants, M22 and M47, on TGF-β-induced transcription. In luciferase assays using 3TP-lux, M47 failed to show inhibitory activity on the TGF-β-induced transcription. In contrast, M22 showed significant inhibition (Fig. 8A). This result confirms the finding by
Mori et al. (43). They concluded that the differential effect of M22 and M47 on TGF-β transcription might be because of their ability to interact with CBP. However, in another study, it has been shown that M47, defective in the COOH-terminal transactivation domain, continued to interact with CBP/p300 (48). They also used a Tax mutant (K88A) defective for the CBP/p300-binding domain, and a KID-like domain in Tax is responsible for the recruitment of CBP/p300 (48). Tax K88A failed to repress transcription from the plasminogen activator inhibitor-1 promoter (43). They suggested that the CBP/p300-binding domain of Tax is involved in the suppression of Smad transactivation function. Because it is known that Smad2, -3, and -4 bind to CBP/p300, and these interactions are promoted by treatment with TGF-β (49–52), Tax may inhibit TGF-β signaling by competing for Smad-CBP/p300 interaction as suggested by Mori et al. (43). However, the competition for Smad-CBP/p300 by Tax cannot explain why Tax M47 fails to repress the Smad transactivation activity even though it still interacts with CBP/p300. In this study, we have shown that M47 does not interact with Smad3 and could not block binding of the Smad complex to its target sequence (Figs. 8 and 9). These results may explain why M47 failed to repress TGF-β transcription activity. Taken together, our observations clearly demonstrate that Tax interacts with Smads directly and specifically. Our present study and the published literature suggest that Tax may inhibit TGF-β transcription activity through two different mechanisms, competing for Smad-CBP/p300 interaction and binding to Smads directly.

This study demonstrates that HTLV-1 Tax inhibits TGF-β signaling, in part, by interaction with Smad proteins and through blocking binding of the Smad complex to its target DNA sequence. Tax inhibits TGF-β signaling by competitive interactions with both Smad proteins and p300. This decrease in TGF-β signaling likely provides the optimal conditions for tumorigenesis in a way that complete abrogation of signaling could not. Significantly, we have shown that inhibition is sufficient to disrupt the growth inhibitory control that TGF-β normally exercises over T lymphocytes. Without one of the most important brakes on their proliferation, these infected cells can then multiply at high rates. But this inhibition of TGF-β signaling is not complete. In particular, our group has previously shown that cell lines overexpressing Tax still respond to TGF-β1 stimulation (18). Treated cells show increased mRNA production for both Tax and, through an autoregulatory loop, TGF-β1 itself. This excess serum TGF-β1, which has been documented in HTLV-1-infected patients (17), then has the potential to significantly alter the function of the remaining normal lymphocytes, most pertinently by diminishing tumor surveillance. With the immune system hampered in its ability to recognize and destroy emerging malignant clones, the increased serum TGF-β1 can enhance tumorigenesis. This considerable inhibition of TGF-β signaling by Tax thus provides a unique favorable environment for the development of T-cell leukemia.

Inhibition of Smad-mediated signaling has been shown to be one of the critical mechanisms for leukemogenesis induced by oncoproteins. An oncoprotein Evi-1 has been shown to interact with Smad3 through its first zinc finger motif and to antagonize the growth inhibitory effect of TGF-β (53). Evi-1 is overexpressed in human myeloid leukemias and myelodysplastic syndromes by chromosomal rearrangements involving 3p26, to which Evi-1 is mapped (54, 55). These findings, together with our findings, suggest a new paradigm that suppression of Smad-mediated signaling may contribute to leukemogenesis associated with oncoproteins.
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