Transcriptional Repression of p53 by Human T-cell Leukemia Virus Type I Tax Protein*

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The human T-cell leukemia virus type I oncoprotein Tax transcriptionally deregulates a wide variety of viral and cellular genes. Tax deregulation of gene expression is mediated through interaction with a variety of structurally unrelated cellular transcription factors, as Tax does not bind DNA in a sequence-specific manner. Although most of these cellular transcription factors have been shown to mediate activation by Tax, we have recently demonstrated that members of the basic helix-loop-helix (bHLH) family of transcription factors, which play a critical role in progression through the cell cycle, mediate repression by Tax. In this report, we examined whether Tax might repress transcription of the tumor suppressor p53, as the p53 gene has recently been demonstrated to be regulated by the bHLH protein c-Myc. Furthermore, loss or inactivation of the p53 gene has been shown to be causally associated with oncogenic transformation. We show that Tax represses transcription of the p53 gene and that this repression is dependent upon the bHLH recognition element in the p53 promoter. Together, these results suggest that Tax may promote malignant transformation through repression of p53 transcription.

Human T-cell leukemia virus type I (HTLV-I) is the causative agent of a highly aggressive T-helper cell malignancy called adult T-cell leukemia (ATL) (1). The virally encoded Tax protein, a potent and highly pleiotropic deregulator of both viral and cellular gene expression, is strongly linked to the oncogenic pathogenesis associated with HTLV-I infection in humans (2–5). Tax appears to be necessary, but not sufficient, for malignant transformation, as only a small percentage of infected individuals develop ATL following a latency period of several decades (6, 7). Together, these observations suggest that Tax may promote malignant transformation in the infected T-cell through the deregulation of cellular genes, possibly including those involved in the control of cell cycle progression.

The mechanism of Tax deregulation of cellular gene expression is not fully understood. Tax does not bind DNA directly (8–11) but instead utilizes cellular transcription factors to deregulate transcription of target genes. Several unrelated cellular transcriptional regulatory proteins appear to mediate activation by Tax, including members of the activating transcription factor/cAMP response element binding protein (ATF/CREB) family, serum response factor, and the NF-κB proteins (for review, see Ref. 1). We have recently demonstrated that Tax repression of gene expression occurs via yet another class of cellular regulatory proteins, the basic helix-loop-helix (bHLH) proteins (12). This family of proteins forms homodimeric and heterodimeric complexes that have differential effects on the expression of genes involved in both cell proliferation and differentiation. The bHLH proteins mediate their effects on cellular gene expression through binding to a consensus DNA recognition sequence (5′-CANNTG-3′), called an E-box, located in the promoter of target genes. These proteins have been grouped into three classes based upon structural characteristics and pattern of expression (13). The class A proteins are ubiquitously expressed and readily bind DNA as either homodimers or heterodimers. Class B proteins are expressed in a tissue-specific manner and form heterodimers with class A bHLH proteins. Finally, class C proteins form homodimers and heterodimers within the class C family and do not form heterodimers with class A or B bHLH proteins. We have previously demonstrated that all three classes of bHLH proteins mediate Tax repression of gene expression upon chimeric promoters carrying E-box sequences (12). However, only a single naturally occurring E-box-containing gene, the β-polymerase gene, has been demonstrated to be a target for repression by Tax (12, 14).

In this study, we investigated whether Tax might repress transcription of the E-box-containing human p53 gene. Wild-type p53 is a tumor suppressor protein that induces either apoptosis or cell cycle arrest at the G1-S checkpoint in response to DNA damage, thus preventing the transmission of genetic mutations to the daughter cells (15, 16). The overall function of wild-type p53 therefore appears to be maintenance of the genetic integrity in the cell. Loss of wild-type p53 activity has been identified in over half of the human malignancies examined (17), consistent with a role for p53 in genome surveillance and the suppression of oncogenic transformation. Because of these critical tumor-suppressive properties of p53 and the fact that chromosomal abnormalities are commonly observed in leukemic T-cells derived from ATL patients, we hypothesized that Tax down-regulation of the p53 gene in an HTLV-I-infected cell might mimic the effect of mutations or deletions in the gene and therefore play an early role in the development of HTLV-I-associated malignant transformation. Furthermore, the p53 gene appeared to be a strong candidate for transcriptional repression by Tax, as the human p53 promoter carries an E-box element and is transcriptionally regulated by the bHLH protein c-Myc (18).

Here we report that the HTLV-I Tax protein represses expression of p53. We demonstrate that Tax repression is dependent upon the p53 promoter E-box element and is mediated by the class C bHLH proteins c-Myc and JUN. Mutations in the
E-box element abolish activation by c-Myc and USF, as well as repression by Tax of p53 expression. Together, these results suggest that Tax repression of this critical tumor suppressor gene in an HTLV-I-infected T-cell may lead to loss of cell cycle arrest following DNA damage, thus promoting the genome instability that may be the trigger for neoplastic transformation.

**EXPERIMENTAL PROCEDURES**

Recombinant Plasmids—The CAT reporter plasmid p1CAT contains a 2.4-kbp restriction fragment from the human p53 gene promoter (19). This promoter fragment carries a single E-box element, CAGTG, which maps from position –29 to –34 relative to the major transcription start site (18, 20). This E-box has previously been demonstrated to bind the c-MycMax heterodimer in vitro (21) and mediate transcriptional activation by c-Myc in vivo (18). The CAT reporter plasmid pTCCAT carries the 2.4-kbp promoter fragment from the p53 gene, with a dinucleotide mutation introduced into the E-box element (TCTGTG) (18). The p53 reporter plasmids were tested in the presence and absence of the Tax expression plasmid, HTLV-I Tax (4), c-Myc expression plasmid, pSP-c-Myc (23), and USF expression plasmid, pLTR-USF (24).

Cell Culture and Transfections—CV-1 cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum and 2 mM L-glutamine. Transient co-transfection assays were performed by calcium phosphate precipitation. Cell lysates were assayed for CAT activity, and the percent of acetylated 14C-labeled chloramphenicol was determined by Phosphor imaging quantitation.

**RESULTS**

To test whether the HTLV-I Tax protein represses expression of the human p53 gene, we performed transient co-transfection assays using the wild-type p53 promoter-CAT reporter plasmid, p1CAT. p1CAT carries the 2.4-kbp promoter fragment from the human p53 gene and includes the c-Myc-responsive E-box located between positions –29 and –34 (18). Transfection assays were performed in CV-1 cells in the presence and absence of plasmids expressing c-Myc, USF, and/or Tax. Co-transfection of the HTLV-I Tax expression vector with p1CAT produced a 2.5-fold decrease in p1CAT expression (Fig. 1A, compare lanes 1 and 2 with 3 and 4). As shown previously, the addition of the c-Myc expression vector stimulated expression from p1CAT 2.5-fold (18) (Fig. 1A, compare lanes 1 and 2 with 5 and 6). c-Myc stimulation of p1CAT expression was observed in a dose-dependent fashion (data not shown, and see Ref. 18), occurring presumably through heterodimerization with endogenous Max protein (23). The introduction of the Tax expression vector in the presence of c-Myc did not further stimulate but produced an even greater-fold repression of p1CAT expression than observed in the absence of cotransfected c-Myc (5-fold) (Fig. 1A, compare lanes 5 and 6 with 7 and 8), bringing expression of the p53 promoter to the same base-line level. Significantly greater Tax repression was consistently observed in the presence of the cotransfected c-Myc expression vector, suggesting that c-Myc or a heterodimeric complex containing c-Myc may directly mediate the repression of p53 by Tax. Transfection of an expression vector encoding a basic region deletion mutant of c-Myc that fails to bind DNA had no effect on expression from the p53 promoter and did not inhibit repression by Tax (data not shown). These data suggest that Tax repression observed either in the absence of transfected c-Myc or in the presence of a non-functional c-Myc mutant may be occurring through endogenous c-Myc or through other related class C bHLH proteins.

To test this idea, we examined whether the related class C bHLH protein USF might also mediate repression of p53 by Tax. USF shares both DNA binding specificity and some structural characteristics with c-Myc and has been shown to transactivate the murine p53 promoter through an analogous E-box sequence (24). In view of this, we hypothesized that USF may also mediate transcription activation, as well as Tax repression, of the human p53 gene. Fig. 1A shows that cotransfection of a USF expression plasmid produced a 2.5-fold increase in p1CAT expression (compare lanes 1 and 2 with 9 and 10) and an approximately 5-fold repression of p1CAT in the presence of the cotransfected Tax expression plasmid (compare lanes 9 and 10 with 11 and 12).

The results presented above demonstrate that HTLV-I Tax represses expression of the p53 CAT reporter construct and suggest that the repression is mediated through the class C bHLH proteins. Since all of these class C proteins bind to a CANNTG motif, elimination of this motif would be predicted to eliminate both transactivation by these proteins and repression by Tax. To test this prediction, we examined the p53 promoter-CAT construct pTCCAT that carries a double point mutation in the single class C E-box element (wild type, CATGTG; mutant, TCTGTG) (18). This mutated p53 promoter construct has previously been shown to appropriately express the CAT gene; however, the E-box double mutation renders the p53 promoter unresponsive to cotransfected c-Myc (18). Fig. 1B shows a transfection experiment with pTCCAT in the presence of the c-Myc, USF, and Tax expression plasmids. Consistent with Roy et al. (18), we did not observe activation of the mutant p53 promoter in the presence of cotransfected c-Myc (compare lanes 1 and 2 with 5 and 6). We obtained essentially identical
results with cotransfected USF expression plasmid (compare lanes 1 and 2 with 9 and 10). Most importantly, introduction of the Tax expression plasmid did not repress pTCCAT activity when transfected in either the absence (compare lanes 1 and 2 with 3 and 4) or in presence of cotransfected bHLH proteins (compare lanes 5 and 6 with 7 and 8 and compare lanes 9 and 10 with 11 and 12). These data provide strong support for the role of class C bHLH proteins, such as c-Myc and USF, in mediating Tax repression of the p53 gene. Furthermore, they demonstrate that repression by Tax occurs through the single E-box element in the p53 promoter.

We were concerned that the observed repression of p53 expression in the presence of Tax might be due to a phenomenon called squelching (25), where high levels of cotransfected activator proteins have been shown to repress expression of certain genes through sequestration of coactivators away from the promoter. To test this possibility, we analyzed Tax activation of the HTLV-I promoter (pU3RCAT) in parallel with Tax repression of the p53 promoter, using a wide range of Tax expression vector amounts. Under conditions where Tax stimulated CAT expression driven by the HTLV-I promoter, we did not observe activation of p1-CAT expression (Fig. 2). The absence of p53 activation at low concentrations of Tax suggests that p53 is not a target for Tax activation and that the observed repression is not due to squelching. Furthermore, these data demonstrate that p1-CAT repression is not due to Tax toxicity in the transfected cells, as parallel amounts of the Tax expression vector consistently produced strong activation from the HTLV-I promoter-CAT construct.

DISCUSSION

The HTLV-I-encoded Tax protein both activates and represses transcription. This deregulation of gene expression is mediated through several distinct classes of cellular DNA binding proteins, as Tax does not bind DNA in a sequence-specific manner. While a wide variety of structurally unrelated cellular DNA binding proteins have been identified as targets for Tax activation, the bHLH proteins are the only cellular proteins identified to date as targets for Tax repression (12). Since the human p53 gene was recently demonstrated to be transcriptionally regulated by the bHLH protein c-Myc, we examined whether c-Myc might mediate Tax repression of p53. We provide data showing that Tax does repress transcription of the human p53 promoter and demonstrate that this repression is dependent upon the single c-Myc binding site in the p53 promoter. Together, these data indicate that Tax may down-regulate transcription of p53, resulting in reduced levels of this important tumor suppressor protein in HTLV-I-infected T-cells.

To determine whether the endogenous p53 gene is repressed in HTLV-I-infected cells, we examined p53 mRNA and protein levels in a panel of HTLV-I-infected (SLB-1, MT-2, C816645, HUT 102) and uninfected (Jurkat, Sup T1, CEM, MOLT 4, HUT 78) cultured human T-cell lines, as well as in the Tax-inducible Jurkat T-cell line JPX-9 (26) (data not shown). Unfortunately, we have been unable to detect a correlation between Tax expression and reduced amounts of p53. Although this observation is inconsistent with the CAT assay data presented here, it is possible that the transformed cell lines do not accurately reflect the consequences of Tax expression in an HTLV-I-infected T-cell in vivo. For example, we have noted that the amount of Tax expression plasmid needed in the transfection assay to observe repression is significantly higher than that needed for activation (see Fig. 2). It is therefore conceivable that the concentration of Tax in the HTLV-I-transformed cell lines is not sufficient to repress p53 expression and that in vivo only intermittent bursts of Tax expression produce levels high enough to down-regulate p53 expression. Alternatively, the class C bHLH protein levels may be significantly elevated in these cultured cell lines, thus masking Tax and uncoupling repression. Consistent with this interpretation, we have observed a relationship between the amounts of Tax and bHLH expression vectors in the transfection reaction. For example, Tax repression is reduced in the presence of high levels of the c-Myc expression vector, and full repression can be subsequently restored by increasing the amount of Tax expression vector (data not shown). These observations are consistent with a stoichiometric relationship between Tax and bHLH proteins in the cell and suggest that high levels of c-Myc may abolish repression by Tax. Finally, it is important to bear in mind that Tax repression of p53 is likely an early event that precedes cellular transformation and is therefore no longer relevant in the transformed cell lines. In fact, increasing evidence suggests that transformed cell lines may not accurately reflect the genetic alterations observed in the parent tumor tissue. For example, mutations in p53 have been found in approximately 30% of Burkitt's lymphoma biopsies versus approximately 65% of the Burkitt's lymphoma cell lines examined (27, 28).

If Tax represses the endogenous human p53 gene in vivo, it likely plays an important role early in the development of the HTLV-I-associated leukemia, ATL. The p53 gene encodes a tumor suppressor protein involved in maintaining the genetic integrity of the cell. Consistent with this, somatic mutations in the p53 gene are strongly implicated in the etiology of sporadic human malignancies, and germ line mutations in p53 are associated with a number of inherited cancers (29–31). Furthermore, loss of p53 function in knockout mice correlates with a high incidence of malignant T-cell lymphomas (32). Since p53 maintains genetic integrity of cells by controlling progression through the cell cycle and inducing apoptosis in response to DNA damage, the loss of p53 function appears therefore to be associated with increased genetic instability and the accumulation of mutations, which likely precede oncogenic transformation.

Reduced levels of p53 in an HTLV-I-infected cell would thus lead to suppression of cell cycle arrest, leading to rapid progression through the cell cycle without the requisite DNA damage repair prior to genomic replication. This condition may be particularly detrimental in an HTLV-I-infected cell, as DNA damage would likely be more extensive due to Tax repression of the DNA damage repair gene, β-polymerase (12, 14). Tax repression of p53 may also inhibit apoptosis, leading to the continued growth of infected T-cells carrying an increased burden.

**Fig. 2. Tax repression of p53 is not due to squelching.** Transient co-transfection assays were performed in CV-1 cells using 4 μg of the HTLV-I LTR reporter plasmid pU3RCAT (22) or 10 μg of the p53 CAT reporter plasmid (p1CAT) (18). Increasing amounts of the Tax (HTLV-I-Tax) (4) expression plasmid were added to each reaction as indicated. The percent acetylation is shown in the figure. This experiment is representative of greater than four trials. We have also examined significantly lower amounts of the HTLV-I expression plasmid and have not under any conditions observed activation of p1CAT.

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of potentially oncogenic mutations. In support of this hypothesis, a recent study suggests that both HTLV-I-infected and Tax-expressing transformed cells are resistant to Fas-induced apoptosis (33). These findings are consistent with the idea that Tax repression of p53 may indirectly inhibit programmed cell death, a condition clearly advantageous to the provirus. Together, the downstream consequences of Tax repression of p53 would likely produce an environment in the HTLV-I-infected cell that would allow the slow accumulation of deleterious mutations, consistent with the development of adult T-cell leukemia following a protracted latency period.

If Tax repression of p53 expression is sufficient to suppress the activities of the tumor suppressor, thus allowing accumulation of oncogenic mutations, we would predict p53 mutations would not play a significant role in the development of ATL. Consistent with this prediction, examination of four HTLV-I-infected patients carries mutations, consistent with the development of adult T-cell leukemia following a protracted latency period.

This study is one of the first to demonstrate an effect on p53 transcription by a viral regulatory protein. Several DNA tumor viruses have previously been shown to directly interact with p53 protein, functionally disabling p53 in the infected cell and possibly contributing to virus-dependent transformation. However, this study and another recent study (36) suggest that retroviruses may differ from DNA tumor viruses by influencing p53 transcription rather than directly interacting with the p53 protein. In their recent report, Li et al. (36) show that the human immunodeficiency virus (HIV) transactivator protein Tat transcriptionally represses p53 expression in T-cells and suggest that this repression by Tat may contribute to HIV-associated pathologies. While Tat and Tax likely differ in their mechanisms of p53 transcriptional repression, it is intriguing that both of these distinct human retroviruses appear to have evolved strategies to repress expression of this important tumor suppressor gene.

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