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Human T cell leukemia virus type 1: the role of Tax in leukemogenesis

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Summary

Human T cell leukemia virus type 1 (HTLV-1) is a complex human retrovirus which is the causative agent of adult T cell leukemia (ATL). ATL occurs in about 4% of carriers and develops after a long latent period. Although the precise mechanism of HTLV-1 oncogenesis remains unclear, the pathogenesis has been linked to the pleiotropic activity of the viral transcriptional activator protein Tax. Tax has been shown to regulate viral and cellular gene expression and to functionally interfere with proteins involved in cell-cycle progression and DNA repair. This review will focus on the role of Tax in p53 inhibition.

Key words:

T cell • leukemia • Tax protein

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INTRODUCTION

The human T cell leukemia virus type 1 (HTLV-1) is a complex retrovirus associated with two fatal human diseases: adult T cell leukemia (ATL) and the neurodegenerative disease tropical spastic paraparesis/HTLV-1-associated myelopathy (reviewed in ref.^{9, 37, 69, 114, 159}). ATL is an aggressive lymphoproliferative disease which can be classified into distinct clinical subtypes: pre-ATL, the acute form, the sub-acute or smoldering form, the chronic form, and ATL lymphoma^{14, 150}. HTLV-1 is endemic in areas of Southern Japan, the Caribbean basin, inter-tropical Africa, the Middle East, South America, and Papua New Guinea¹⁴. It is estimated that 20–30 million people worldwide may be infected with HTLV-1. Of those, about 4% will go on to develop disease after a latency of 20 or more years¹¹³.

In vivo, HTLV-1 infects CD4⁺ peripheral T cells, but has also been detected, to a lesser extent, in CD8⁺ T cells^{78, 133, 177}. Unlike typical transforming retroviruses, HTLV-1 does not encode a cellular oncogene or disrupt cellular gene regulation by insertional mutagenesis. While several viral proteins act in concert to allow infected cells to avoid immune regulation, modulate anti- and proapoptotic signals, and increase T cell responsiveness to extracellular stimuli, the viral Tax protein is the major viral oncoprotein^{49, 161, 172}.

GENOMIC STRUCTURE AND GENE EXPRESSION

HTLV-1 is a complex Delta-retrovirus whose genome encodes structural and enzymatic proteins: Gag, Env, reverse transcriptase, protease, and integrase³⁵. In addition, HTLV-1 has a region at the 3' end of the virus, called pX, which encodes four partially overlapping reading frames (ORFs) (Fig. 1). These ORFs code for regulatory proteins which impact the expression and replication of the virus.

While much work has focused on the regulation of Tax and Rex in viral replication and expression, recent studies have pointed to a role for the accessory proteins in T cell activation, transcriptional regulation, viral persistence, and immune evasion^{4, 5, 37}.

The p12^I protein, which bares sequence similarity to the E5 protein of bovine papilloma virus type 1, is a small hydrophobic protein which localizes to the golgi and endoplasmic reticulum (ER)^{5, 32, 74}. Although not necessary for HTLV-1 replication *in vitro*, p12^I was shown to contribute to viral infectivity *in vivo* using a rabbit animal model system^{4, 26, 27, 86}. Later studies have linked p12^I to T cell activation. p12^I has been shown to increase signal transducers

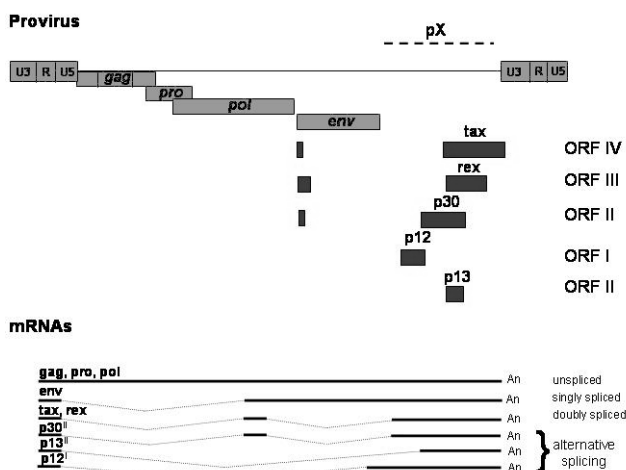


Figure 1. Genomic structure of HTLV-1. The upper panel is a diagrammatic representation of the structure of the HTLV-1 proviral DNA and encoded genes. The lower panel shows the structure of the unspliced and spliced mRNA species.

and activators of the STAT5 pathway, increasing DNA binding and transcriptional activity in T cell lines as well as primary T cells¹¹⁹. In agreement with having a role in T cell activation/proliferation, p12^I also interacts with both calnexin and calreticulin, ER-resident proteins which regulate calcium storage and increase calcium release³².

The ORF II region of the viral mRNA encodes the p30 and p13 accessory proteins. When the p30 protein is expressed ectopically, it is found to localize to the nucleus and nucleoli of transfected cells⁸². The p13 represents the C-terminal 87 amino acids of p30. Ectopic expression of p13 localizes it to the nucleus and mitochondria^{24, 25, 82, 83}. While little is known about the function of p13, a mitochondrial targeting signal at its amino terminus and the observation that its expression alters the mitochondrial inner membrane potential suggest it may play a role in apoptosis^{24, 25, 82}.

As is the case with the p12^I protein, indirect evidence suggests the expression of p30 in infected cells. Antibodies and cytotoxic T cells to p30 have been found in HTLV-1-infected individuals¹²⁷. In addition, using a molecular clone in which expression of both p30 and p13 has been ablated, investigators found a role for these proteins in viral infectivity in a rabbit model^{13, 153}. However, *in vitro* expression of p30 and p13 is dispensable for infection and immortalization of primary human T cells³⁰. More recently, a role for p30 in maintaining viral latency has been proposed. Because p30 is capable of binding p300/CBP, Zhang et al.¹⁷⁹ suggested that p30 is a negative regulator of gene expression in a mechanism involving p300/CBP

squelching. In addition, Nicot et al.¹¹⁸ and Younis et al.¹⁷⁸ proposed that p30 negatively regulates virus production by binding to and retaining the tax/rex mRNA in the nucleus. This reduction in viral replication may allow escape from immune recognition and thus viral persistence.

The viral Rex and Tax proteins, on the other hand, have been shown to positively regulate virus production. The Rex protein acts posttranscriptionally. Rex binds viral mRNA, facilitating its export from the nucleus and expression of the viral structural and enzymatic proteins^{57, 62, 148}. The transforming ability of the virus has been attributed to the viral Tax protein. Tax activates both viral and cellular gene expression, facilitating cell growth and ultimately leading to viral immortalization/transformation^{103, 176}.

PLEIOTROPIC FUNCTIONS OF TAX

Tax is a 40-kDa phosphoprotein that is predominately nuclear, but has been shown to shuttle between the nucleus and cytoplasm¹⁸. Tax lacks a cellular homologue³⁷, but has been shown to transactivate or transrepress the expression of a wide number of cellular genes (Fig. 2). These include cytokines, growth factors, cellular receptors, cell-cycle regulators, DNA repair proteins, or proteins which regulate apoptosis (reviewed in ref.^{37, 176}). Tax does not bind DNA directly but acts through cellular transcription factors, CREB, NF- κ B, and serum-responsive factor (SRF)^{37, 176}.

With the advent of DNA microarray technology, profiles of HTLV-1-infected cells and Tax-expressing

cells have allowed a more complete list of HTLV-1/Tax-regulated genes^{53, 117, 131}. It is these pleiotropic actions of Tax that predict its central role in leukemogenesis (Fig. 2).

Tax-mediated activation of the CREB/ATF-dependent transcription

Tax was originally identified as a transcriptional activator for viral gene expression. Tax drives viral gene expression from three imperfect 21-base-pair repeat enhancer elements located within the U3 region of the HTLV-1 long-terminal repeat (LTR). Each Tax-responsive element (TRE) contains a core CREB/ATF binding site flanked by 5'G- and 3'C-rich residues^{17, 68}. Tax efficiently activates the LTR by forming a Tax/CREB/TRE complex where binding of Tax to CREB enhances CREB homodimer formation^{47, 89, 98, 124, 175, 176}. Tax is believed to contact the G-C-rich flanking sequences of the DNA, which results in a conformational change in Tax allowing the exposed C-terminal region of Tax to recruit the coactivators CBP/p300 and PCAF^{80, 93}. Unlike CREB-mediated transcription, Tax-mediated transcription occurs in the absence of CREB phosphorylation. The ability of Tax to activate transcription via CREB/ATF sites is context specific, since transcriptional activation of cellular promoters that contain CREB sites is not seen^{1, 89, 156}.

Tax-mediated activation of the SRF-dependent transcription

Tax-expressing cells exhibit an increased expression of immediate early genes, such as c-fos, c-jun, JunB, JunD, c-egr, and Fra-1^{41, 162}. These proteins are members of the dimeric transcription factors AP-1, Egr-1 and Egr-2, and fra-1, which are normally activated by the SRF in response to a variety of mitogenic signals⁵⁶. SRF binds to the SRF-responsive element contained in the promoters of these genes. Tax interacts directly with amino acids 422 to 435 of SRF^{40, 42}. This interaction enhances the transcription of select promoters containing the CarG box motif⁴³. Further, Shuh and Derse¹⁵¹ have shown that transcriptional activation of the SRF pathway by Tax requires recruitment of CBP/p300.

Tax-mediated activation of the NF- κ B-dependent transcription

Tax works at several levels to maintain constitutive activation of the NF- κ B pathway⁶⁰. Although a direct interaction between Tax and different members of the NF- κ B family have been reported, the primary action of Tax in activating NF- κ B has been shown to

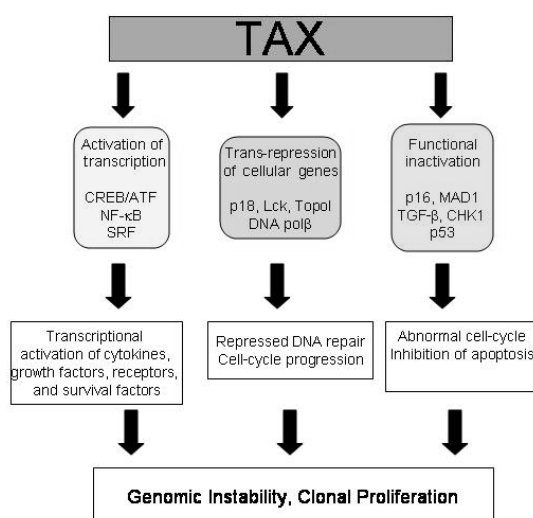


Figure 2. The pleiotropic effects of Tax. This is a summary of the activity of Tax within an infected cell that leads to uncontrolled cell proliferation.

occur through interaction with IKK γ in the IKK signalosome, which includes IKK α , IKK β , NIK, and MEKK1. A more comprehensive discussion of this topic can be found in reviews on Tax activation of NF- κ B^{11, 60, 67}.

CELLULAR TRANSFORMATION

The long latent period that precedes the onset of ATL suggests a multistep mechanism of leukemogenesis¹²³. Two major ways in which viral oncoproteins affect the passage of cells through individual phases of the cell-cycle are by 1) increasing the expression level of growth-promoting genes and 2) altering the function of cell-cycle regulatory proteins.

Several studies have established that Tax expression is both necessary and sufficient to establish the transformed phenotype. Examination of malignant cells from ATL patients which carry defective HTLV-1 proviral genomes suggests the genomes preferentially retain the 3' end of the proviral genome encoding the Tax protein^{84, 122}. Several other lines of evidence more directly demonstrate the importance of Tax in cellular transformation. Using a *Herpes virus saimiri* vector, expression of the 3' portion of the HTLV-1 genome containing the Tax gene was able to transform T cells, resulting in a phenotype similar to HTLV-1-transformed cells⁴⁹. Mutation of the start codon of Tax eliminated cellular transformation⁴⁸. Rodent fibroblastic cell lines expressing Tax form colonies in soft agar and tumors in nude mice¹⁶¹. Tax also immortalizes rat embryo fibroblasts and cooperates with *ras* in cellular transformation¹³⁵. Subsequently, Smith and Greene¹⁵⁴ found that Tax alone could transform Rat2 cells. In addition, Tax expression allows factor-independent growth of established murine T cell lines⁶⁵.

In transgenic mice, Tax protein expressed from the HTLV-1 LTR gave rise to animals which developed neurofibromas and mesenchymal tumors^{28, 116}. In addition, arthritis and thymic atrophy have been observed⁶⁴. To investigate Tax's leukemic potential, Grossman et al.⁵⁰ targeted Tax to the mature T lymphocyte compartment by developing mice which express Tax under the control of the granzyme B regulatory element. While these mice did not develop CD4⁺ T cell leukemia, they did develop large granular lymphocytic leukemia of a natural killer cell and cytotoxic T lymphocyte nature⁵⁰.

Enhancing T cell proliferation

As indicated above, Tax has been shown to regulate the expression of a number of cellular genes

(reviewed in ref.^{9, 37, 176}). Indeed, DNA microarray studies indicate that Tax directly or indirectly regulates hundreds of genes^{53, 117, 131}. Many of these are known to be involved in T cell proliferation, such as interleukin (IL)-2, the α chain of IL-2 receptor (allowing for an autocrine loop), IL-15 and its receptor IL-15R, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α ^{9, 37, 44, 69}.

In addition to activating autocrine growth, Tax also inhibits the activity of the growth-inhibiting cytokine TGF- β ^{8, 90, 110}. While Tax has been shown to increase transcription from the TGF- β promoter¹²⁰, cells are resistant to its growth-inhibitory effects⁶¹. This resistance is due to the many effects of Tax on the TGF- β signaling pathway. First, Tax directly competes with TGF- β for binding of the coactivators p300/CBP such that TGF- β cannot activate the Smad proteins^{8, 90, 110}. Second, Tax can interact with some of the Smad proteins, preventing their interaction with CBP/p300⁹⁰. Finally, Tax works downstream on the TGF- β -responsive protein p15 by interfering with its cell-cycle arrest function through direct interaction^{55, 79}.

Tax can further disrupt cell-cycle progression by impacting the function of cyclin/cyclin-dependent kinase (cdk) proteins (reviewed in ref.^{37, 44, 69, 176}). Cyclin/cdk complexes control the progression of cells through various stages of the cell-cycle. Although the levels of the cdks remain constant, the levels of cyclins fluctuate throughout the cell-cycle^{29, 149}. Tax can increase the levels and activity of several cyclin/cdk partners which control the G1 to S progression (Fig. 3). Tax increases the transcription of cyclins D1, D2, and D3 and increases the kinase activity of cdk2, cdk4, and cdk6^{2, 52, 109, 144, 147}. In addition, Tax has been shown to enhance cdk4/cyclinD2 binding, resulting in an accumulation of hyperphosphorylated Rb⁵². Hyperphosphorylated Rb releases E2F, allowing it to actively promote transcription of a number of genes required for S phase transition^{85, 155, 173}.

Disruption of DNA repair and cell-cycle control

As with other viral oncoproteins, Tax has the capability of disrupting several points in the cell cycle (Fig. 3). One of the first indications that Tax has an effect on DNA repair came with the finding that Tax inhibits the activity of DNA polymerase β ⁷⁰, an enzyme involved in base excision repair and mismatch repair. More recent studies have shown that Tax interferes with several modes of DNA repair, such as base excision repair, nucleotide excision repair, and mismatch repair^{76, 77, 92, 101}. Suppression of these functions likely increases the genomic mutation rate and contributes to cellular transformation. Indeed, a wide range of

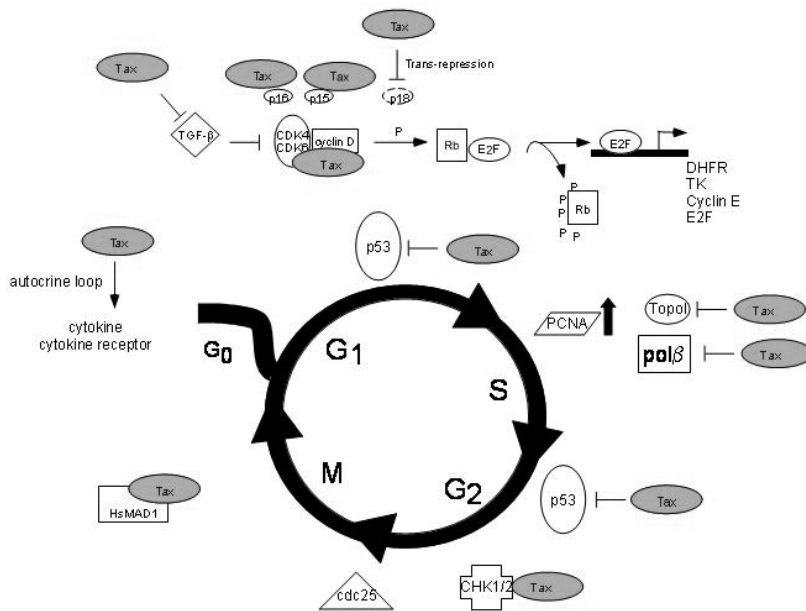


Figure 3. Dysregulation of the cell-cycle. This is a schematic representation of the points in the cell-cycle affected by the HTLV-1 Tax protein. Tax has been shown to increase the expression of a number of cytokines and cytokine receptors allowing T cell proliferation. Cyclin D/CDK activity regulates the progression through G1. Tax increases cyclin D/CDK activity and the levels of PCNA, while inhibiting the negative regulators p15, p16, p18, and TGF- β , thus allowing progression through the G1 and S phases of the cell-cycle. Because Tax can inhibit the activity of p53 and CHK1 proteins, the G1/S and G2/M checkpoint functions are impaired. Tax has also been shown to inhibit the activity of Topoisomerase I (TopoI), DNA polymerase β (pol β), and human MAD1 (HsMAD1), all of which play a role in cell-cycle regulation. A more in-depth review of this topic can be found in Gatza et al.⁴⁴.

chromosomal abnormalities have been found in HTLV-1-transformed lymphocytes isolated from patients^{23, 107}. In addition, cells expressing Tax have been shown to be more susceptible to mitomycin C-induced DNA damage and exhibit a significant increase in micronuclei formation^{102, 141}.

While mutations may occur, eukaryotic cells have developed signaling pathways to coordinate cell-cycle transitions and ensure faithful replication of the genome before cell division. These regulatory pathways are termed cell-cycle checkpoints²⁹. Checkpoints exist in cells to interrupt cell-cycle progression when damage to the genome or spindle is detected, or when cells have failed to complete an event. When a checkpoint is triggered, cells arrest transiently to allow for the repair of cellular damage or, alternatively, if damage is irreparable, signal pathways lead to programmed cell death. The ability of normal cells to undergo cell-cycle arrest or apoptosis is critical for the maintenance of genomic integrity. Defects in cell-cycle checkpoints can result in gene mutations, chromosome damage, and aneuploidy, all of which may contribute to tumorigenesis.

TUMOR SUPPRESSOR P53

Arguably the most frequently detected alteration in human cancer is inactivation of the tumor suppressor, p53. In fact, mutation of p53 is associated with approximately 50% of all human cancers. In addition, p53 is a frequent target for inactivation by viral transforming proteins such as SV40 large T-antigen, HPV E6, hepatitis B X-antigen, and adenovirus E1A and E1B¹³⁶. While Tax has been shown to affect several cell-cycle

checkpoints such as G1/S and DNA repair^{37, 44, 176}, this review will focus on the role of Tax in p53 inhibition.

p53 function

The p53 protein belongs to a family of related proteins that includes two other members, p63 and p73^{15, 164}. While the proteins are all structurally and functionally related, p63 and p73 have clear roles in development, whereas p53 seems to have evolved to prevent tumor development and has earned the name “cellular gatekeeper”.

Several stress signals can activate p53, triggering a variety of responses including cell-cycle arrest, differentiation, DNA repair, apoptosis, or senescence

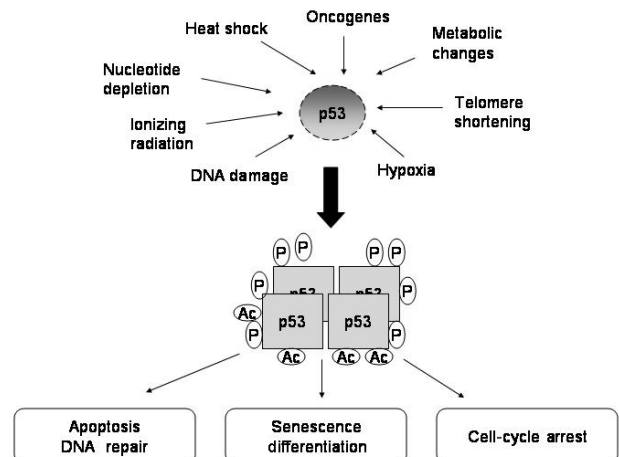


Figure 4. The p53 response. Diagrammatic representation of the central role p53 plays in the coordination of the cellular response to a variety of stresses. Abbreviations Ac and P represent acetylation and phosphorylation, respectively.

(Fig. 4). There are five recognized domains in p53, which include the N-terminal transcriptional activation domain, the proline-rich domain, the sequence-specific DNA-binding domain, the tetramerization domain, and the basic regulatory domain. p53 functions as a tetrameric, sequence-specific DNA-binding transcription factor that controls the expression of an array of gene products in response to diverse stress stimuli.

p53 is extensively phosphorylated, and modification at several residues have been specifically associated with the ability of p53 to respond to certain stress signals. There are numerous phosphorylation sites in the N-terminal domain and phosphorylation of serines 15, 20, and 37 and threonine 18 have been shown to regulate p53/MDM2 interaction *in vitro*. The kinases signaling to p53 include casein kinase 1 and 2, ataxia telangiectasia kinase (ATM), ATR (ATM/Rad3-related kinase), CHK1 and 2, jun N-terminal kinase, and DNA-dependent protein kinase (reviewed in ref.^{6, 168}). Several of these kinases have also been shown to phosphorylate MDM2 *in vitro* within the p53-binding domain, further suggesting a regulatory role for these modifications¹⁶⁸.

Under damage or stress conditions, the phosphoacceptor sites are modified through a regulated kinase cascade *in vivo* (^{6, 168} and references therein). It is the complexity and combination of the phosphorylation sites that appears to dictate the fate and function of p53. For example, the phosphorylation pattern of p53 differs during the cell-cycle and coincides with the ability of p53 to associate with regulatory proteins, including p300 and MDM2^{33, 87}. In addition, *in vitro* protein-protein interaction assays demonstrated that phosphorylation at serine 15 alone inhibited the interaction of p53 with TBP¹³². In contrast, phosphorylation at serines 15 and 37 did not inhibit TBP binding, suggesting that the combination of phosphorylated sites is important.

In addition to its complex phosphorylation pattern, p53 is acetylated on at least 3 lysine residues: 320, 373, and 382^{51, 95, 142}. Additional C-terminal lysines have also been identified as potential acetylation sites. Acetylation of p53 has been implicated in transcriptional regulation by p53 and its association with basal transcription machinery^{51, 95, 142}. In addition, association of p53 with deacetylases has implications for regulating both p53 transcriptional activation and repression functions^{10, 169}.

p53 in HTLV-1-infected cells

HTLV-1 infection is associated with stimulation of G1- to S-phase progression¹⁴⁷. Because p53 plays

such a key role in G1- to S-phase transition, several groups have examined the status of p53 in HTLV-1-infected cells. Early observations found that p53 was wild-type in sequence, but stabilized in most HTLV-1-infected T cells^{137, 174}. For those cells having p53 mutations, they appeared to correlate with late stages of disease^{121, 143}. In 1996, Cereseto et al.²⁰ demonstrated that p53 was transcriptionally impaired in ATL cells. In addition, these cells failed to undergo G1 arrest after induction of DNA damage.

Biochemical studies of p53 in HTLV-1-infected cells demonstrated that p53 existed primarily as tetramers¹³², which reside in the nucleus. Using biotinylated oligonucleotides or gel mobility shift assays it was shown that p53 from transformed cells can bind DNA in a sequence-specific manner^{112, 132}. Interestingly, in the transformed cells, p53 was found to be hyperphosphorylated at serines 15 and 392 by phosphopeptide mapping¹³². This observation was of significant interest since, as discussed above, the pattern of p53 phosphorylation is significantly altered in response to stress^{6, 168} and in human tumors¹⁰⁵. Moreover, the phosphorylation of p53 is predicted to alter its conformation and its association with other factors. This may explain why p53 is inactive in tumor cells despite its wild-type genotype¹⁴⁶.

Viral oncoproteins such as SV40 large T-antigen or adenovirus E1B¹³⁶ have been shown to directly bind to p53 inactivating its function. Several groups have shown by immunoprecipitation or *in vitro* pull-down assays that Tax protein does not bind to p53^{7, 112, 132}. It appears more likely that Tax inhibits p53 function through an indirect mechanism. The indirect mechanism, however, results in a similar phenotype to E1B since the p53 in the transformed cells does not interact with the basal transcription factor TFIID¹³². Interestingly, decreased TFIID binding correlated with phosphorylation of p53 at serine 15^{33, 132}, suggesting that Tax regulates the p53 through modulation of upstream kinase activity or specificity.

In normal non-stressed cells, p53 has a very short half-life due to a negative feedback loop mechanism in which MDM2 protein plays a key role (reviewed in ref.¹⁰). Transcription of MDM2 is upregulated by p53. In turn, MDM2 directly binds to p53 and functions as a ubiquitin E3 ligase that promotes the conjugation of ubiquitin to p53, resulting in its proteasome-mediated degradation. The importance of this negative feedback loop is illustrated by the result that MDM2 null mice are not viable unless crossed to p53 null mice¹⁰⁸. Consistent with the stabilization of p53 in HTLV-1-infected cells, MDM2 binding to p53 was not detected¹³². In related studies, Takemoto et al.

found that p53 stabilization and functional impairment in HTLV-1-transformed cells occurred in the absence of genetic mutation or alteration of the p14 ARF-MDM2 loop¹⁵⁸.

MECHANISMS OF TAX-MEDIATED P53 INHIBITION

Several groups have shown that of the HTLV-1-encoded proteins, expression of Tax protein alone is sufficient to inhibit p53 transcriptional activity. Transient transfection assays demonstrated that Tax could inhibit p53 activity constructs^{112, 128}. Similar observations were reported in stable T cells expressing only Tax³.

The mechanism by which Tax inhibits p53 function is not completely understood, but much progress has been made. There is general agreement that Tax-mediated p53 inhibition is not through direct binding of Tax, altering p53 sub-cellular localization, or disrupting DNA binding. However, there is controversy as to whether Tax uses the NF- κ B or CREB/ATF pathway to inhibit p53 function. Our studies point to the activation of the NF- κ B pathway as being important for Tax-mediated p53 inhibition^{100, 129}. In other studies, Tax activation of the CREB/ATF pathway was reported to play a role in p53 inhibition^{7, 112, 130, 166}. A partial resolution of the apparently discrepant results was offered by Pise-Masison et al.¹³⁰, who reported that the mechanism was cell-type dependent and depended largely on the intracellular pool of CBP/p300. More recently, an indirect mechanism of p53 inactivation by Tax has also been proposed because of the interaction of Tax with the hTid-1 protein, which is a human homologue of the *Drosophila* tumor-suppressor protein Tid56²².

NF- κ B pathway

Although other pathways have been implicated^{140, 154}, strong evidence supports the activation of the NF- κ B family of eukaryotic transcription factors by Tax as playing a critical role in HTLV-1-induced leukemia^{65, 138, 139, 154}. This is not surprising, since the NF- κ B family plays an important role in the regulation of immune responses, embryonic and cellular development, apoptosis, cell-cycle progression, inflammation, and oncogenesis.

An early study showed that while antisense oligonucleotides to Tax had no effect on tumor growth, antisense to NF- κ B blocked Tax induced tumor growth⁸¹. More recently, using the infectious molecular clone of HTLV-1, Robek and Ratner¹³⁸ demonstrated that mutants of Tax that could not activate the NF- κ B pathway could not immortalize human T lympho-

cytes. In contrast, Tax mutants which failed to bind p300/CBP or activate the HTLV-1 LTR still allowed lymphocyte immortalization^{138, 139}. Similarly, inhibition of apoptosis induced by factor withdrawal in mouse CTLL cell lines correlates with the ability to activate NF- κ B and induction of the anti-apoptotic, NF- κ B-regulated gene, BCL_{xL}^{65, 163}. Further, inhibition of NF- κ B activity by expression of the NF- κ B2 precursor abrogated Tax-mediated transformation of rat fibroblasts without affecting viral LTR activation¹⁷¹. Using Tax-transgenic mice, Portis et al.¹³⁴ demonstrated that salicylate and cyclopentenone prostaglandins, inhibitors of NF- κ B activity, blocked spontaneous proliferation of Tax transgenic mouse spleen cells. In addition, Tax-induced tumor cells resistant to irradiation-induced apoptosis became sensitive in the presence of sodium salicylate and prostaglandins.

In addition, our laboratory has found a strong link between Tax's ability to activate NF- κ B and its ability to inhibit p53 in lymphocytes¹²⁹ (Fig. 5). Blocking NF- κ B activation by expressing a dominant negative I κ B α protein blocks Tax-mediated p53 inhibition not only in Tax-transfected cells, but also in HTLV-1-transformed cells^{72, 129}. Since expression of exogenous p300 could not rescue p53 activity, squelching of the coactivator by Tax or NF- κ B appears not to be responsible for the block in p53 transcriptional activity in these studies¹²⁹.

Our present evidence suggests that p65/RelA is uniquely involved in p53 inhibition. Antisense oligonucleotides to p65, but not p50 or c-Rel, restored p53 activity in transformed cells⁷². In addition, p50 null cells allowed Tax-mediated p53 inhibition, but p65 null cells could not support inhibition of p53 by Tax unless the p65 subunit was added back^{72, 129}. In the presence of Tax protein, p65 appears to inhibit p53 transactivation function by direct interaction with p53. p65/p53 complexes were detected in HTLV-1-infected and Tax-transfected cells by co-immunoprecipitation. Previous studies suggest a strong link between the ability to phosphorylate p53 at serines 15 and 392 with the ability of Tax to inhibit p53 transactivation of both reporter constructs and endogenous genes¹²⁹. Likewise, Tax-induced binding of p65 to p53 correlated with the phosphorylation status of p53.

Modifications of p65 may also play a role in p53 binding and inhibition. Recent reports indicate that p65 can be both phosphorylated and acetylated, and these modifications influence the protein's ability to be recruited to the transcriptional apparatus and stimulate target gene expression¹⁶⁷. Inducible p65 phos-

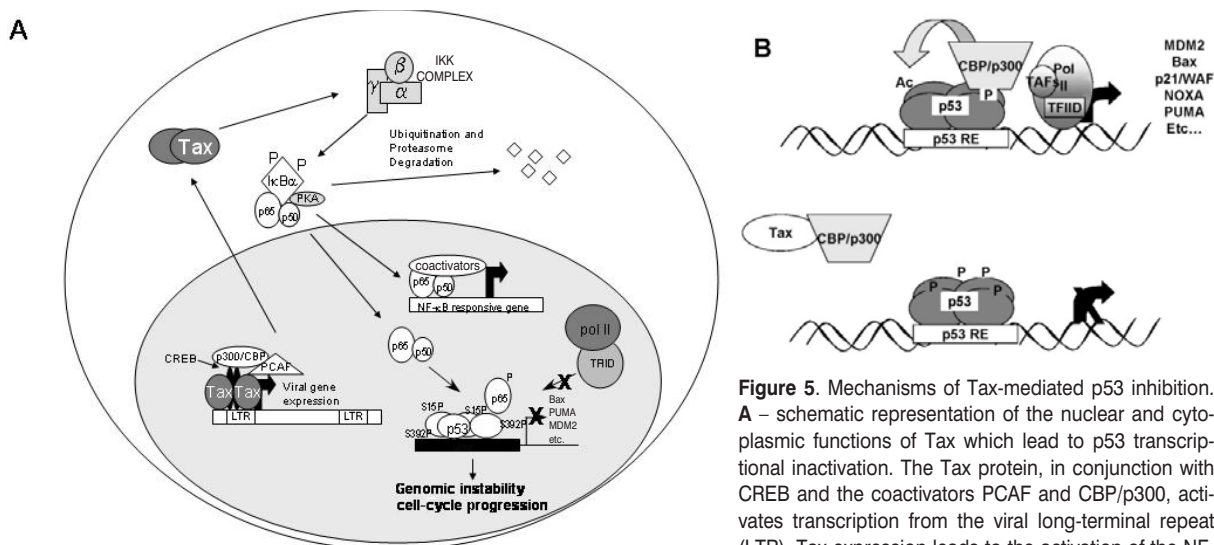


Figure 5. Mechanisms of Tax-mediated p53 inhibition. **A** – schematic representation of the nuclear and cytoplasmic functions of Tax which lead to p53 transcriptional inactivation. The Tax protein, in conjunction with CREB and the coactivators PCAF and CBP/p300, activates transcription from the viral long-terminal repeat (LTR). Tax expression leads to the activation of the NF-κB pathway through the IKK signalosome. This activa-

tion leads to nuclear translocation of the NF-κB transcription factor, which in turn activates NF-κB-responsive genes involved in proliferation and cell survival. Tax expression also leads to the phosphorylation of p53 at serines 15 and 392. This phosphorylation contributes to the binding of the NF-κB subunit p65/RelA to the p53 protein. Although p53-p65 complexes are found bound to p53-responsive promoters *in vivo*, the basal transcription machinery is not recruited to the promoter. This results in the inhibition of p53 transcriptional activity. **B** – binding of the coactivators p300/CBP to p53 protein have been implicated in p53 transactivation. Once bound to p53, p300/CBP can acetylate lysine residues in the carboxy-terminal region of p53, enhancing its sequence-specific DNA-binding. The viral Tax protein is also capable of binding p300/CBP and can compete with p53 for binding, resulting in inhibition of p53 transcriptional activation function. RE refers to responsive element.

phorylation has been found in both the C-terminal transactivation domain and the Rel homology domain¹⁶⁷. Studies are in progress to determine the importance of p65 phosphorylation in Tax-mediated p53 inhibition. Indeed, Jeong et al.⁷¹ recently found that the kinase activity of the upstream IKK complex plays an important role in p53 inhibition by Tax. Further, a strong link to p65 phosphorylation and p53 inhibition is seen.

It is of interest then to identify which components of the transcription factors are associated on the active and inactive p53-responsive promoters. To this end, chromatin immunoprecipitation assays show that in HTLV-1-transformed cells, p53/p65 complexes bind to the MDM2 promoter. Consistent with the results of DNA pull-down assays¹³², TFIID was not found on the promoter⁷². In contrast, these same studies showed that in cells in which p53 was transcriptionally active, p53/TFIID complexes, but not p65, were found on the promoter. Studies are underway to fully characterize the active and inactive promoter complexes.

These studies identify a unique mechanism for p53 regulation by the p65/RelA subunit of NF-κB. The role of p65 in directly inhibiting transcriptional activity has also been proposed for the glucocorticoid receptor (GR). Two groups have recently shown that a direct interaction between p65 and GR result in mutual transcriptional inhibition^{104, 170}. Further, while

p300/CBP may function as an integrator of p65/GR physical interaction, it is not a limiting cofactor for which p65 and GR compete^{104, 170}. Rather, similar to the proposed model for p53/p65, p65 disturbs the interaction of GR with the basal transcription machinery irrespective of the coactivator levels. Further studies are required to determine what factors govern the interaction and subsequent promoter inhibition of Tax-mediated p53/p65 complexes.

CREB/LTR activation pathway

In other situations, p53 inactivation occurs through direct competition between Tax and p53 for recruitment of coactivators p300/CBP (Fig. 5B). CBP and p300 are highly homologous coactivators that promote gene expression by bridging DNA-bound transcription factors and the basal transcription machinery, providing a scaffold for integrating transcription factors, and by modifying transcription factors and chromatin through acetylation^{21, 45, 66}. Evidence indicates that interference with normal CBP/p300 function can result in a variety of diseases^{21, 45, 66}. CBP haplo-insufficiency is the hallmark of Rubinstein-Taybi syndrome, and chromosomal translocations affecting the p300 and CBP genes are the cause of congenital malformations and hematological malignancies¹²⁵. In addition, mutations in the CBP or p300 gene, accompanied by loss of the other allele, have been found in a variety of cancers^{21, 45, 66}.

Many factors, including Tax, steroid and retinoid hormone receptors, phospho-CREB, c-Jun, c-Myb, NF- κ B, TBP, and p53, have been found to interact with CBP and/or p300^{21, 66}. Studies have shown that Tax mutants such as K88A and V89A, which fail to interact with CBP/p300⁵⁴, failed to inhibit p53 transcriptional activity^{7, 130, 165}. *In vitro* binding assays demonstrated that Tax interferes with the recruitment of CBP to DNA-bound p53¹⁵⁷ and that Tax and p53 binding to GST-C/H1-KIX were mutually exclusive¹⁶⁵. Similarly, in transient transfection studies, a reciprocal repression between Tax and p53 was seen^{157, 165}. Finally, exogenous p300 could, in certain cell types, rescue p53 activity¹³⁰. Recent studies have also indicated that Tax can inhibit the p53 family members p73 α and p73 β , perhaps also through CBP/p300 squelching^{75, 91}. To note, the Tax mutant M47, which is still capable of binding CBP/p300 but does not activate the viral LTR, failed to inhibit p53 activity^{112, 130, 166}. This suggests that additional factors may be involved.

It is important to note that while competition for coactivators may occur in transient transfection assays where proteins are over-expressed, chromatin immunoprecipitation assays suggest that p300/CBP is present at sufficient levels to bind to both viral and cellular promoters in HTLV-1-infected cells⁹⁷. Chromatin from HTLV-1-transformed Hut-102 cells was cross-linked, fragmented, precipitated with p300 antibody, and the DNA subjected to PCR amplification using primers for the HTLV-1 LTR or IL-15R α promoter. The results of this study clearly demonstrate that p300 is present on both the LTR and IL-15R α promoters⁹⁷.

FUTURE DIRECTIONS

Acute phase ATL carries a very poor prognosis due to the resistance of leukemic cells to conventional or even high-dose chemotherapy. In other human cancers there is a consensus that reactivation of p53 function in cancer cells could be of therapeutic benefit. Indeed, several recent studies have defined small molecules or peptides that restore function to mutant p53 proteins, illustrating the potential of this approach^{19, 36, 38, 39, 88}. As it is becoming clear that the apoptotic and cell-cycle activities of p53 are indepen-

dently regulated, more targeted therapies to regulate cell death-inducing functions of p53 are being pursued. Since the majority of ATL patients harbor a wild-type p53 protein that is functionally impaired, reactivation of p53 could be potentially beneficial in ATL treatment.

In support of this, reports have shown that inhibition of NF- κ B activation with Bay 11-7082 or arsenic trioxide treatment of HTLV-1-infected cells results in apoptosis^{34, 63, 99, 111}. Several reports link p53 activation with arsenic-induced apoptosis and cell-cycle^{73, 94, 96, 180}. Although no change in p53 stability or serine 15 phosphorylation was observed in arsenic-treated HTLV-1-infected cells, p53 may be functionally active in these cells due to decreased p65 binding. It cannot be ruled out at this point that additional events may be important for full activation of p53. Thus, combination therapy may be required. With this in mind, studies using the NF- κ B inhibitor PS-341, which has been successful in the treatment of multiple myeloma and mantle cell lymphoma^{12, 58, 126}, have shown promise.

Indeed, studies examining the effect of PS-341 on HTLV-1-infected cell growth indicate that PS-341 causes apoptosis and cell-cycle arrest in HTLV-1-transformed cells^{115, 145}. Animal models also indicate that PS-341 has an effect on HTLV-1 tumor cell growth. Using a NOD-SCID mouse model for ATL, Tan and Waldmann¹⁶⁰ found that treatment of mice with PS-341 and humanized anti-Tac was associated with a complete remission in a portion of treated animals. Similarly, Mitra-Kaushik et al.¹⁰⁶ found, using Tax-induced tumors transplanted into Rag-1 mice, that PS-341 significantly slowed the growth of the transplanted tumors, increasing survival.

Constitutive NF- κ B activation has been associated with breast, ovarian, prostate, and colon cancers^{16, 31, 46, 59, 152}. In addition, many viruses, including HTLV-1, HIV, hepatitis B virus, hepatitis C virus, and Epstein-Barr virus, and influenza have been shown to activate NF- κ B to promote viral replication, prevent virus-induced apoptosis, and mediate the immune response⁶⁰. It will be important to determine if constitutive NF- κ B activation, specifically p65 expression, is a general mechanism for p53 inhibition in human cancer.

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