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THE HTLV-I TAX ONCOPROTEIN: HYPER-TASKING AT THE MOLECULAR LEVEL

Diane R. Wycuff and Susan J. Marriott

Dept. Molecular Virology & Microbiology, Baylor College of Medicine, Houston, TX 77030

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1. ABSTRACT

HTLV-I is a complex retrovirus that encodes a transcriptional activator, Tax, which regulates expression of the viral promoter. Tax has been shown to be both necessary and sufficient to effect immortalization and transformation of cells in culture and tumorigenesis in animal models. Tax exerts its influence through protein-protein interactions with a variety of molecular targets, including transcription factors and cofactors, histone modifying enzymes and post-translational modifying enzymes. Through these interactions, Tax disrupts cellular regulatory cascades and checkpoints designed to control a variety of systems. The result is untimely activation or repression of gene expression, inappropriate protein modifications, incorrect cell cycling, loss of adequate DNA repair capacity, and potential release of the cell from tumor suppression. Whereas for the virus these functions of Tax provide a means for successful completion of its life cycle, for the cell, they result at best in anarchy, and at worst in death of both the cell and the organism of which that cell is a part.

2. INTRODUCTION TO HTLV-I

2.1. HTLV-I epidemiology

Human T cell leukemia virus type I (HTLV-I) was the first human pathogenic retrovirus identified (1, 2), and was promptly causally linked to a disease that came to be called adult T cell lymphoma (ATL), reviewed by Ratner, this issue. Subsequently, this virus was also associated causally with a neurodegenerative disease, first named tropical spastic paraparesis (TSP), then also named HTLV-I associated myelopathy (HAM), and now referred to by both terms as TSP/HAM (3, 4).

Estimates of numbers of people infected with HTLV-I worldwide vary from 10 to 20 million (5, 6) with infection particularly endemic in parts of the Caribbean, Africa, South America, and Japan, where ATL was first reported and characterized (7) (Figure 1). Of those infected, a predicted 5% will develop disease, most commonly ATL (reviewed in 8), and second most commonly TSP/HAM (reviewed in 9). HTLV-I is statistically responsible for 1% of all leukemias (10). HTLV-I has also been linked with several less debilitating diseases, including infective dermatitis (11, reviewed in 12), rheumatoid arthritis (13, reviewed in 14), uveitis, (15, reviewed in 16), and polymyositis (17, 18). These are generally considered to result from pathological inflammatory responses to the virus (19). They often present in seropositive carriers with no other disease symptoms (19, 20, reviewed in 21). In an individual ATL patient, the viral integration site is clonal within tumor cells, which exist in a background of oligoclonally or polyclonally infected cells (22, 23, 24). No notable commonality in integration sites has been reported in tumor cells (25). Infiltrating infected CD4+ T cells in TSP/HAM patients exist as oligoclonal populations (26, 27). The time from infection to the onset of ATL or TSP/HAM is estimated to be 20 to 40 years (28), and statistical analysis predicts that five independent genetic events subsequent to infection are required for transformation (29).

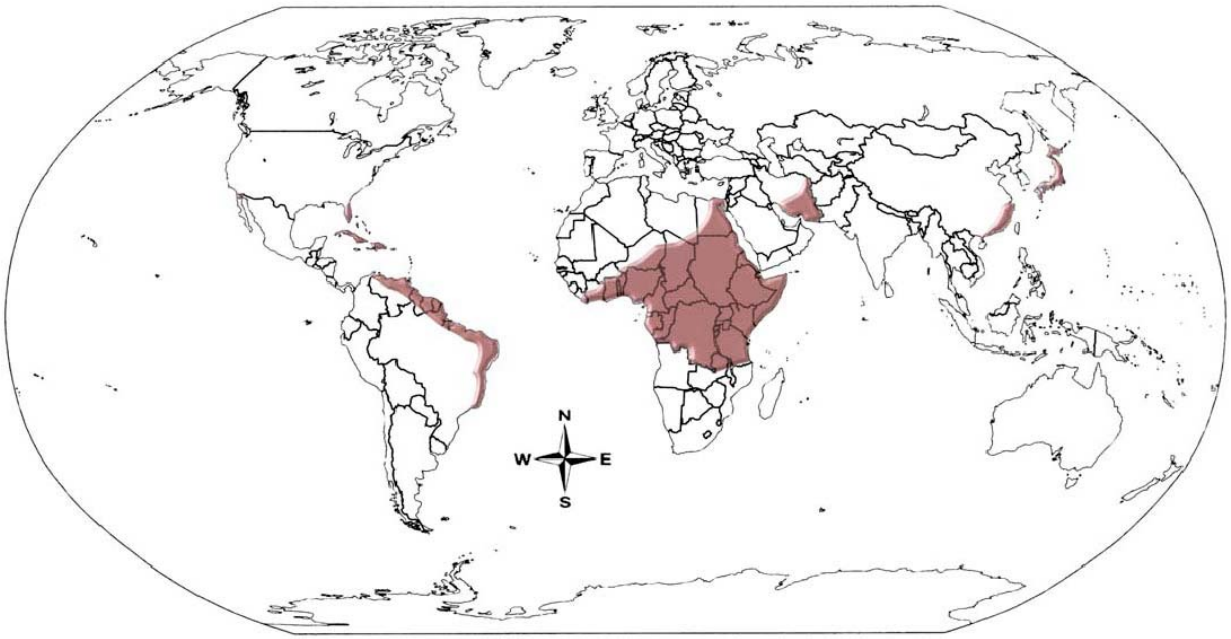

Figure 1. World map depicting regions of endemic HTLV-I infection in brown. HTLV-I infection is particularly prevalent in Japan, parts of South America, parts of Africa, and the Caribbean (modified from 6, 322).

HTLV-I is transmitted from infected mother to child (vertical), between sexual partners, or by contaminated blood products or tissue (horizontal) (30, reviewed in 6). There is a growing body of evidence that infection from mucosal exposure may favor genesis of ATL, whereas exposure through peripheral blood may favor development of TSP/HAM (31, 32). The immunological phenotype of the infected individual also influences disease progression and status (33, 34, 35).

2.2. Geography of the HTLV-I genome

The HTLV-I genome has been completely sequenced (36) and shares characteristics with other retroviruses (Figure 2). Flanked by long terminal repeats (LTRs) on both ends, the genome encodes the common retroviral gag, pro, pol, and env genes in the first 6 kb followed by a unique region at the 3' end of the genome, referred to as the X region, because of an early enigma regarding the function of this region's gene products. Four open reading frames, termed I, II, III, and IV, have now been identified within the X region. Region III encodes the Rex protein (37, 38), see Green *et al.* this issue, and region IV encodes the Tax protein (39, 40). Regions I and II encode proteins termed "accessory" that are referred to as p12 and p30/13, respectively, (41, 42, 43), see Bindhu *et al.* this issue. Alternative mRNA splicing and frameshifting during translation are used by HTLV-I to generate the 12 protein products that have been identified (44, reviewed in 45).

The HTLV-I LTR is divided into three regions, U3, R, and U5 (Figure 3). The 5' LTR serves as the principal viral promoter with a TATA box and binding sites for numerous cellular transcription factors located in the U3 region (46, 47). The transcription start site is located at the border between the U3 and R segments. The LTR also contains three 21 bp repeats called TRE1 (Tax response element 1) with homology to cellular cyclic AMP response element binding protein (CREB) binding sites (CREs). The HTLV-I Tax protein binds to CREB and CREB family members and activates transcription from these elements to high levels (48, reviewed in 49). An additional Tax responsive region, termed TRE2 or ERR-1, is located between the second (middle) TRE1 and the third (promoter proximal) TRE1 (50, 51, 52). It contains additional cellular protein binding sites, and new Tax responsive elements continue to be characterized within this region (53). *In vivo*, the two LTRs, although virtually identical in sequence, appear to be methylated differentially, predominately silencing the 3' LTR. Similarly, hypermethylation of the 5' LTR correlates with latency of viral gene expression (54, 55, 56).

2.3. The HTLV-I life cycle

As is true of retroviruses in general, the mature HTLV-I virion is surrounded by a lipid envelope derived from the membrane of the host cell from which it budded. This envelope projects glycoprotein spikes encoded by the viral *env* gene. There are two *env* gene products, the 21 kDa transmembrane protein (TM) and the 46 kDa surface glycoprotein (SU) (Figure 2). Evidence indicates that retroviral attachment and entry involves interactions between the SU and a host cell surface receptor(s). Recent evidence points to the HTLV-I receptor being a glucose transporter, GLUT-1 (57, reviewed in 58, 59 and Manel *et al.* this issue). There is convincing evidence that the HTLV-I receptor is widely expressed on multiple cell types from a variety of species (60, 61, 62, 63). Since CD4+ T cells are the primary targets of virus infection *in vivo* a coreceptor may be involved in viral attachment and/or entry (62, 63, 64). Binding of SU to the receptor triggers fusion with the cell membrane (62, 65) and T cell activation in a CD2-dependent pathway (66). The reverse transcriptase enzyme, present within the virus capsid, initiates synthesis of viral

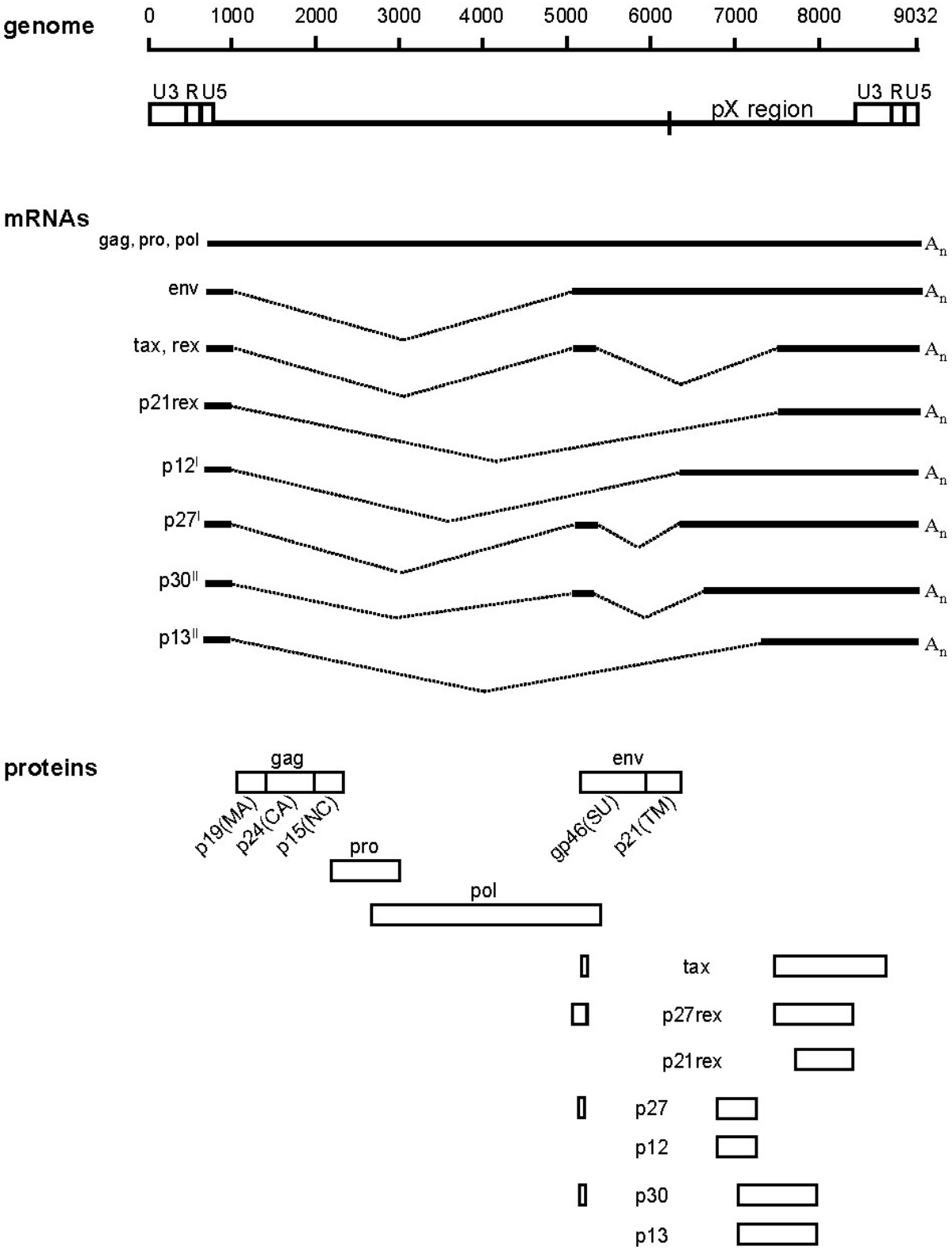

Figure 2. HTLV-I genome organization and gene products. The proviral genome is flanked by direct long terminal repeats and is approximately 9000 bp long. It encodes the retroviral canonical gag, pro, pol, and env genes as well as a number of genes in the pX region, including Tax, Rex, and other accessory proteins. Singly-spliced mRNA results in the env message, p21rex, and p13, whereas doubly-spliced mRNA comprises the full length rex, tax, p30 and p27 messages. Usage of different start codons and frameshifting results in expression of the viral proteins.

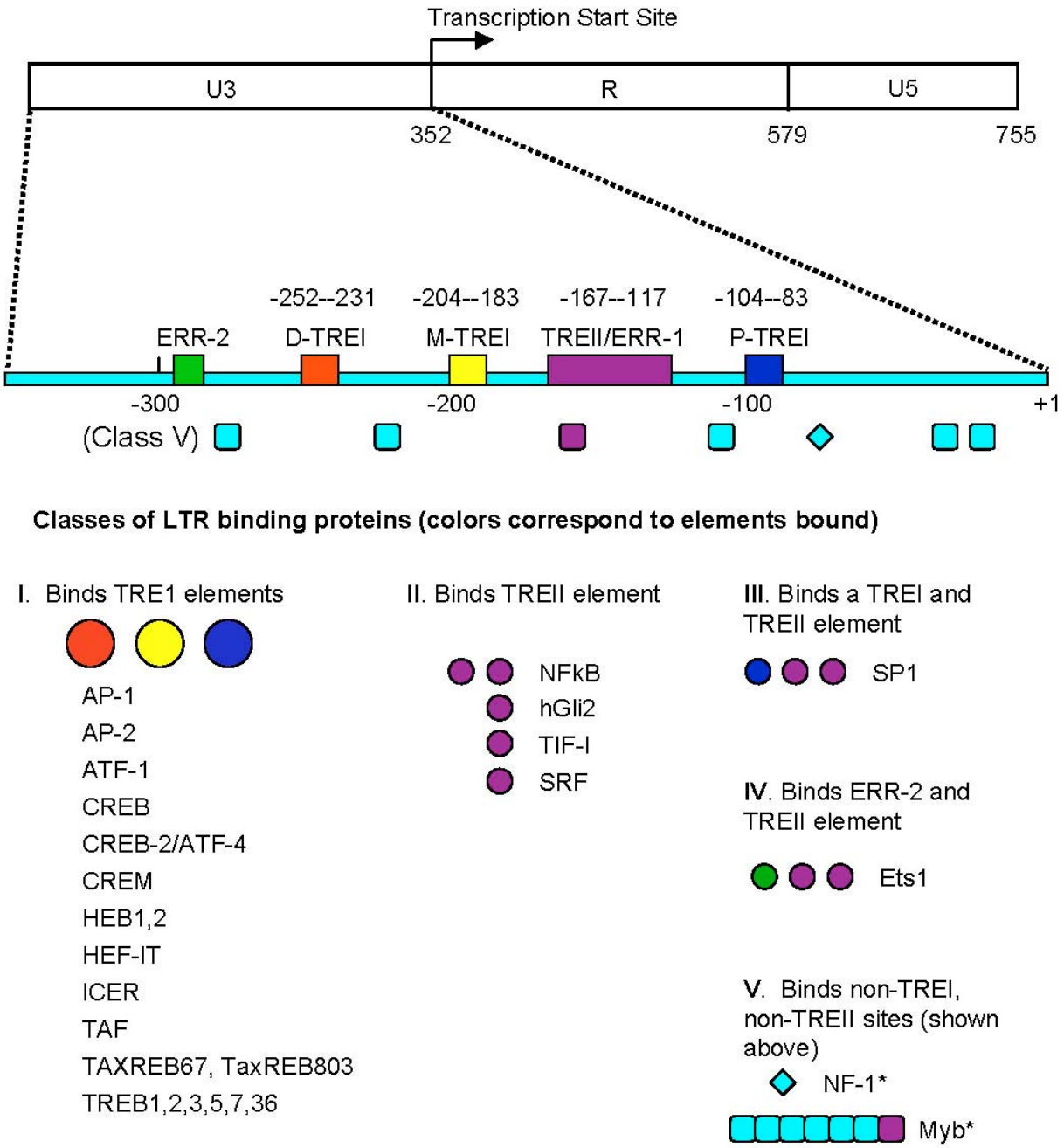

Figure 3. U3 region of the HTLV-I LTR and binding proteins. The LTR region of the HTLV-I genome is depicted and numbered according to genome sequence. Below, the U3 region is expanded, and numbering reflects the designation of the transcription start site at the boundary of U3 and R as +1. The three TRE1s are shown as red, yellow, and blue rectangles, TRE2/ERR-1 as a purple rectangle, and the upstream ERR-2 as a green rectangle. Multiple proteins bind within the U3 region and have been grouped according to which binding sites they associate with. Class I includes TRE1 binding proteins, including multiple members of the ATF/CREB family. Class II includes proteins that bind TRE2. Class III consists of SP1, which binds both to a TRE2 site and to the proximal TRE1. Class IV consists of Ets1, which has two binding sites in the TRE2 and one in the ERR-2. Class V includes two proteins, which have binding sites located either outside or both outside and inside one of the general binding regions. These have been individually designated under the bar that represents the entire U3 region (modified from 323, 324).

progenomic DNA, using genomic RNA as a template. Following viral entry and uncoating, double-stranded viral genomic DNA is transported into the nucleus and integrated into the host cell genome using the enzymatic activity of the viral integrase, also contained within the viral capsid. Early events in HTLV-I infection and replication are reviewed in Derse *et al.* this issue. Following integration, the provirus undergoes replication,

transcription, and translation of its gene products, and virion assembly and release by budding, to complete its life cycle. These processes require cellular as well as viral machinery (67, 68, 69).

3. EFFECTS OF TAX ON GENE EXPRESSION

3.1. Role of Tax in cellular transformation

Early HTLV-I studies demonstrated its ability to infect and immortalize or transform cells in culture (70, 71, 72). Immortalization of peripheral blood mononuclear cells (PBMCs) allows them to grow in culture long-term. In a subsequent step toward transformation, cells acquire the ability to grow in culture in the absence of exogenous IL-2. In addition to PMBCs, a variety of cell types from multiple species have been immortalized or transformed by co-culture with HTLV-I (73, 74, 75, 76). Tax protein has been demonstrated to be responsible for this activity both in transformation assays and in transgenic animal experimental models (70, 75, 77, 78, 79, 80, 81).

The mechanisms by which Tax promotes cellular transformation have been the subject of intense and ongoing investigations that have revealed a protein with extensive pleiotropic effects on host cell replication, transcription, DNA repair, and cell cycling. Tax exerts its functions not as a specific DNA-binding protein, but rather through interactions with cellular transcription factors or other cellular proteins (Table 1) (49, 82, 83, 84, 85). Multiple cellular transcription factor pathways are targeted by Tax; the most comprehensively studied and reported ones include CREB, NF-kappa B and SRF.

3.2. Transcriptional activation through the CREB pathway

Tax interacts with the transcription factor CREB and other members of the CREB family (49, 86) to activate the HTLV-I LTR in the absence of regulated CREB phosphorylation (47, 84). Under normal cellular regulatory conditions, CREB is phosphorylated at a critical serine residue, S133, in response to activating signals (87, reviewed in 88, 89). This modification activates CREB to bind the CREB binding protein (CBP), which functions as a coactivator and subsequently promotes transcription of genes containing a CREB response element(s) (CRE) in their promoters (90, 91). On the viral LTR, Tax bypasses this regulated system by binding CBP and CREB concomitantly, thereby promoting transcriptional activation in the absence of CREB phosphorylation. Conversely, studies on a model cellular CRE have determined that Tax-directed activation requires CREB phosphorylation (92). CBP and its close relative p300 effect their coactivator functions predominantly through their histone acetyltransferase (HAT) activity (93). Therefore, Tax may disregulate cellular gene expression by modulating the enzymatic activity of HAT proteins to which it binds. CBP-Tax-CREB complexes have been identified (92), and residues essential for Tax interactions with both CREB and CBP have been located by mutational analysis (94, reviewed in 95, 96, 97). An additional protein, p300/CBP associated factor (P/CAF) has also been identified in complexes with Tax (98) or with Tax and p300 (99). Although P/CAF also possesses HAT activity (100), this activity is not essential for Tax-directed transcription of the LTR (98).

Collectively, studies examining Tax activation of cellular promoters support its ability to assemble P-CREB, CBP/p300, and/or P/CAF into active complexes under conditions in which CREB would remain inactive in the absence of Tax. The HAT activity associated with these complexes can alter chromosomal architecture at these promoters. Tax is also recruited to the TRE1s within the HTLV-I LTR through interactions with CREB, which can occur in the absence of CREB phosphorylation. The CREB-Tax complex can subsequently recruit CBP, resulting in transcriptional activation in the absence of cellular signaling (92).

3.3. Transcriptional activation through the NF-kappa B pathway

A second target for Tax is the nuclear factor kappa B (NF-kappa B) family of transcription factors. Tax exerts its influence on these factors by a completely different strategy than that elucidated for CREB. The NF-kappa B family consists of at least five related proteins, generally divided into two groups, the first consisting of p105/p50 (NF-kappa B1) and p100/p52 (NF-kappa B2), the second consisting of c-Rel, RelA (p65), and RelB (reviewed in 101, 102, 103, 104). This family of transcription factors regulates expression of a large group of diverse targets, including growth factors such as IL-2 (105, 106), anti-apoptotic proteins such as Bcl (107), TRAF1, TRAF2, c-IAP1, c-IAP2 (108), and the caspase 8 inhibitor FLIP (109), as well as the pro-apoptotic protein p53 (110), but plays an especially large role in activating genes involved in the immune response.

Under quiescent conditions, NF-kappa B is sequestered in the cytoplasm in an inactive complex with one of the inhibitor of kappaBs (I kappa B), a family of proteins that includes the p105 and p100 proteins mentioned above, which in their precursor forms, function as inhibitors (101). Upon stimulation, I kappa B is phosphorylated by IKK proteins (inhibitors of kappa kinases) at two amino-terminal serine residues (111, 112, 113, 114), causing it to be targeted for ubiquitination and proteolysis with the concomitant release of NF-kappa B and its translocation into the nucleus (115, 116). A second event, phosphorylation of one of the second group of NF-kappa B proteins (RelA, RelB, or c-Rel) is necessary for NF-kappa B -directed transcriptional activation (117, 118). Tax expression results in nuclear, active NF-kappa B in the absence of these regulatory steps (119). Tax disrupts NF-kappa B regulation by at least two strategies. By interacting with MEKK1 kinase, which normally phosphorylates the IKKs in a regulated fashion, Tax promotes constitutive IKK phosphorylation (120). Subsequently, targets of the IKKs, the I kappa Bs, are phosphorylated and degraded (121). Tax also interacts directly with IKKs to increase their kinase activity (122, 123, 124), thereby inducing constitutive I kappa B phosphorylation, dissociation of I kappa B and NF-kappa B, and translocation of NF-kappa B into the nucleus (125).

3.4. Transcriptional activation through the SRF pathway

Serum response factor (SRF) represents the third

Table 1. Cellular Genes Whose Expression Patterns are Changed by Tax

Gene	Effect on Expression	Path	Category of Gene Product Function	References
1309	+		CC chemokine	222
Act2/MIP-1beta	+		Beta chemokine	222, 223
Bax	-	E box	Apoptosis regulator	224
Bcl-xl	+	NFκB CREB	Anti-apoptosis	225, 226, 227
beta-1, 4-N-acetylgalactosaminyl-transferase	+		Ganglioside synthesis	228
b-myb	-		Transcription factor	229
Butyrate Response Factor	+	CREB	mRNA degredation	230
CalpainII	+		Cysteine protease	231
c-fos	+	SRF	Transcription factor	137, 136
c-jun	+		Transcription factor	232
c-myb	-	NFκB	Transcription factor	233, 234
c-myc	+	NFκB	Transcription factor	235
c-Rel	+	NFκB	Transcription factor	236, 237
c-sis/PDGF-beta	+	SP1 SP3 Egr1	Protein tyrosine kinase	238
CXCR4	+	nuclear respiratory factor1	Cell surface receptor, cell fusion	239
Cyclin A	-	CREB	Cell cycle	240
Cyclin D1	+	NFκB	Cell cycle	200
Cyclin D2	+	NFκB CREB	Cell cycle	241, 242, 200
Cyclin D3	-	CREB	Cell cycle	240
DNA pol alpha	-	CREB	DNA replication	240
DNA polymerase beta	-	E box	DNA repair; BER	154, 243
E2F-1	+	CREB	Cell cycle transcription factor	244
E-cadherin	+	NFκB	Cell adhesion	245
Egr-1	+	SRF	Transcription factor	138
Egr-2	+	SRF	Transcription factor	138
ETR101	+	CREB	Putative Transcription Factor	246
FasL	+	NFκB CREB NFAT	TNF receptor family ligand; apoptosis induction	247, 248
Fibronectin	+	NFκB	Cell surface glycoprotein; cell adhesion	249
Fra-1	+	AP1 Rb control element	Transcription factor, cell motility	250
Fucosyltransferase VII	+	CREB	Synthesis cell surface glyco-moieties	251, 252
Galectin-3	+	NFκB CREB	Galactose and IgE binding	253
GM-CSF	+	NFκB	cytokine	254,255,256,257
HTERT	-	c-Myc	DNA polymerase	258
ICAM	+	CREB	Cell adhesion	259, 260, 261
IL-1alpha	+	NFκB	Cytokine	262, 263
IL-1beta	+	C/EBPβ Spi-1 PU.1?	Cytokine; pyrogen	264
IL-2	+	NFκB AP1	Cytokine	254, 265, 266
IL-2Ralpha	+	NFκB	Cytokine receptor	267,190,257,268
IL-4	+	C/EBPβ	cytokine	269
IL-6	+	NFκB	Cytokine	262, 270, 270
IL-8	+	NFκB AP1	CXC chemokine	222
IL-10	+	NFκB	Anti-inflammatory cytokine	271, 272
IL-13	+		cytokine	273
IL-15	+	NFκB	Cytokine	274
IL-15Ralpha	+	NFκB	Cytokine receptor	275
iNOS	+		Immune and inflammatory modulator	276, 277, 278
interferon (IFN) consensus sequence- binding protein (ICSAT)	+		Transcription factor; IRF family member	279
IP-10	+		Interferon inducible inflammation regulator	222
IRF-4	+	NFκB NFAT	Transcription factor; T cell activation	280, 281
Lck	-	E box	Protein tyrosine kinase	282, 146
Lyn	+		Protein tyrosine kinase	283
Matrix Metalloproteinase 9 (MMP9)	+	NFκB SP1	Degradation of extracellular matrix	284
MIP-1alpha	+		CC chemokine	222, 285
monocyte chemoattractant protein (MCP)-1,	+	NFκB	chemokine	286, 287
MultiDrugResistance-1	+	C/EBPβ	Transmembrane transport	288, 289, 290
Nerve Growth Factor	+	CREB-like	Neuron growth, differentiation	291
NF-1	-		GAP family member, regulates Ras activity	47
Nur77	+	CREB AP1	Steroid receptor; apoptosis related	292, 293
Ox40	+	NFκB	TNF family member; cell surface receptor	294, 295
Ox40L	+	NFκB	Transmembrane ligand	296, 297, 298
p18INK4C	-	E box	Cyclin dependent kinase inhibitor	211
p19INK4D	-		Cyclin dependent kinase inhibitor	95
p21Cip	+	E box	Cell cycle; kinase inhibitor	217, 299
p27Kip	-		CDK inhibitor	95
Parathyroid hormone-related protein (PTHrP)	+	SP1 Ets1	Regulatory for calcium metabolism	300, 301, 302, 303, 304
PCNA	+		DNA replication and repair	160, 166
Proenkephalin	+	AP1	Neurotransmitter/Neuroimmodulator	305, 306
SCM-1/SCYC-1	+		C chemokine	222
Stat 1	+		Signal transduction; transcription factor	307
Stat 5	+		Signal transduction; transcription factor	307
TGFbeta	+		Proliferation & differentiation	308, 309
Thioredoxin	+		oxidoreductase	310
tissue inhibitors of matrix metalloproteinases-1 (TIMP-1)	+	AP1	Connective tissue remodelling	311
TNFalpha	+	NFκB	Proinflammatory cytokine	312, 313, 314
TNFbeta	+	NFκB	Proinflammatory cytokine	315, 316
VA-1	+	CREB		317
V-Cam	+	NFκB	Cell adhesion	318
Vimentin	+	NFκB	Cytoskeletal subunit	319, 320
Zap-70	-		Protein tyrosine kinase; T cell activation	321

and least well-characterized cellular transcription factor pathway targeted by Tax. Serum response factor is a MADS box-binding protein and was first identified as a transcription factor activated in response to serum (126,

127, 128). Since its activation is independent of *de novo* protein synthesis, SRF is categorized as an immediate early gene (129). Multiple targets of this transcription factor have been identified and include genes important in early responses to mitogenic stimulation, as well as genes important during early stages of development, particularly in myogenesis in general (130, 131, 132, 133) and cardiomyogenesis in particular (134, 135). Following mitogenic stimulation SRF is phosphorylated, resulting in its activation. Tax usurps this pathway by interacting with SRF and perhaps cofactors in a strategy that resembles that employed for CREB activation. The interaction of Tax and SRF results in constitutive expression of early growth response genes including *c-fos*, *egr1*, and *egr2* (83, 136, 137, 138, 139). Roles for cofactors or histone modifying proteins in this activation have not yet been reported. Binding sites for multiple proteins, including CREB and SRF, have been identified within the HTLV-I LTR (47, Wycuff *et al*., in press). Dysregulated activity of an immediate early protein such as SRF may provide a mechanism by which HTLV-I can promote productive infection and/or reactivation from viral latency.

3.5. Transcriptional repression

In addition to gene activation, Tax also represses the expression of a variety of genes, primarily those containing E boxes in their target promoters (Table 1). E boxes are binding sites for the E2A family of proteins, which includes c-Myc (140), E47, and E12 (141). The E2A transcription factors are important in T cell and B cell development (142, 143, 144). Tax does not interact with E47, but in the presence of Tax, the association of E47 with p300 is decreased and transcription of E47-dependent genes is repressed. The repression of E box-containing genes correlates with the ability of Tax to bind p300 (145). Some genes whose expression is repressed by Tax do not possess E boxes, including *NF-1* and *lck* (146, 147). In these cases, Tax may squelch gene expression by similarly interacting with a requisite cofactor for that promoter, thereby precluding promoter activity.

Using the above-described strategies and no doubt others as well, Tax disrupts the regulation of cellular gene expression, resulting in alterations in cellular processes including cell cycle regulation, DNA replication and repair, and apoptosis, leading to immortalization, transformation and leukomogenesis. The ability of Tax to disrupt careful regulatory systems in place for these processes is consistent with cell survival in the presence of mutations and aneuploidy that would normally trigger cellular self-destruction.

4. IMPACT OF TAX ON DNA REPAIR

DNA can be damaged either through intracellular mistakes during replication or as a consequence of extracellular environmental stresses. Not surprisingly, cells possess extensive and intricate mechanisms that detect and repair such damage. If repair is not possible, cellular systems exist to prevent errors from being transmitted to daughter cells. DNA repair can be classified into four categories, nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), and recombination repair, based on the type of damage recognized and repaired and the proteins involved (reviewed in 148). To date, Tax has been reported to disrupt two of these pathways, NER and BER, and there is no experimental evidence that Tax directly causes DNA damage (149).

4.1. Impact of Tax on base excision repair

BER removes damaged bases from DNA, which can result from spontaneous events or exposure to exogenous agents such as ionizing or UV radiation. These agents cause base modifications that, along with apurinic/apyrmidinic sites, are repaired by BER. Apurinic/apyrimidinic sites are one of the most frequent DNA lesions incurred by the genome (150). During BER, nucleotides are inserted by a specific repair enzyme, DNA polymerase beta (pol beta) (151, 152, 153), and the first intimation that Tax might influence the stability of cellular DNA came from reports that Tax suppressed expression of DNA pol beta (154). Subsequent work demonstrated that Tax does indeed impede BER (155). The predominant type of BER is short patch, involving insertion of a single nucleotide by DNA pol β beta (151, 152), but long patch repair, involving insertion of up to 10 nucleotides, occurs in 25% of BER events (156), and is proliferating cell nuclear antigen (PCNA)-dependent (153, 157, 158, 159). Although it has been shown that Tax activates PCNA expression (160), the effects of Tax-induced PCNA over-expression on BER have not yet been reported. The function of another important BER protein, p53, is also impacted by Tax expression, which could contribute to Tax inhibition of BER. The effects of Tax on p53 and vice versa are covered in a companion review (see Pise-Masison and Brady this issue).

4.2. Impact of Tax on nucleotide excision repair

Tax also disrupts the NER pathway of DNA repair (161, 162). NER repairs bulky DNA adducts such as pyrimidine dimers. NER proceeds by two pathways, global genomic repair, which repairs general lesions, and transcription-coupled repair, which occurs when the transcription machinery encounters a transcription-blocking lesion (163, 164). The disruption of NER by Tax (165) correlates with Tax-induced activation of PCNA expression (166). The PCNA protein is intimately associated with DNA and with DNA polymerases delta and epsilon, which function in DNA repair and replication. When DNA damage is detected, p21 levels increase, and p21 interacts with PCNA, blocking its role in DNA replication but not DNA repair (167, 168). It is proposed that upon Tax transactivation of the PCNA promoter, increased levels of PCNA overcome the p21-induced replication block, enabling replication in the presence of damage (168), which would result in incorporation of unrepaired lesions into the genome. Additional evidence suggesting that Tax affects DNA repair comes from a report that Tax co-localizes with Chk2 and p53BP1, proteins involved in DNA damage recognition and repair (169). It is possible that Tax affects the function of these proteins by abrogating their participation in damage recognition and repair.

4.3. Impact of Tax on aneuploidy

In addition to clastogenic lesions, aneuploidy is a

hallmark of malignant cells in general and of ATL cells specifically (170), as well as of HTLV-I cells infected *ex vivo* (171, reviewed in 172). One explanation of this phenotype may lie in the ability of Tax to bind to the mitotic arrest deficiency 1 protein (MAD1) (173). MAD1 is part of the mitotic spindle assembly checkpoint (MSC), as are several other proteins, including budding uninhibited by benzimidazole (BUB1, 2, and 3) (174), MAD2, and MAD3 (175). Since MAD1 transcription is regulated by p53 (176, 177), Tax may also impact MAD1 activity by inactivating p53 (178, 179, 180). Both hBUB and hBUBR1 have been reported to be mutated in a high proportion of ATL patients (181), and the MSC has been found to be defective in a study of HTLV-I infected cell lines in which MAD1 and MAD2 mislocalized from the nucleus to the cytoplasm (182). Because MAD1 function is required to direct MAD2 to the kinetochores (183), by altering MAD1 function, Tax also disrupts MAD2 function. Since MAD2 functions to block activity of the anaphase-promoting complex (184, 185, reviewed in 186), these Tax-driven events may promote progression of the cell through mitosis and cell division, even in the presence of chromosomal lesions. Thus, the impact of HTLV-I on DNA damage repair is likely the result of Tax's influence on transcription and its sequestration of repair factors through protein-protein interactions.

5. TAX AND CELL CYCLE REGULATION

5.1. Activation of cell cycling

Quiescent cells enter the cell cycle from G0 upon mitogenic stimulation by a variety of factors or events. Continued presence of growth factors is important from early through late G1. As described above, Tax activates the expression of genes required to initiate and promote cell proliferation. These include SRF, Egr1, and Egr2, early proteins in cell activation (136, 187). Tax also activates the expression of IL-2 and IL-2R-alpha, the high affinity subunit of the IL-2 receptor, through NF-kappa B elements in their promoters (188, 189, 190). In a newly infected cell, these high levels of IL-2 and IL-2R-alpha insure that the cell is activated and moves through the cell cycle, with a concomitant increase in the nucleotide pool needed for cellular DNA synthesis and viral replication.

5.2. Retinoblastoma protein

Despite the fact that Tax acts at multiple points in the cell cycle, for example, disrupting M phase as described above, many studies investigating the influence of Tax on the cell cycle have focused on G1. In normal cells the retinoblastoma tumor suppressor protein (Rb) plays a key role in the control of cell cycle progression. During the G1 phase, Rb is hypophosphorylated, a state that enables it to bind to the transcription factor E2F with high affinity and precludes activation of E2F-responsive promoters, including those of cyclin E, important for progression through G1 phase, and cyclin A, important for progression through S phase (191). Cyclins, complexed with their partners, cyclin-dependent kinases (cdks), progressively phosphorylate a host of proteins necessary for cell cycle progression, including Rb itself. Resultant Rb hyperphosphorylation releases E2F, thereby inducing additional cyclin expression.

In its hypophosphorylated state, Rb recruits a histone deacetylase (HDAC) to E2F binding sites (192, 193, 194), which provides additional downregulation of expression from E2F regulated promoters by causing local histone deacetylation, augmenting E2F sequestration. Rb also recruits the human homologues of the yeast SWI/SNF complexes, BRG1 and hBRM, to these promoters to modulate chromosome architecture at these sites (195). In early G1, cyclinD/cdk4 complexes phosphorylate Rb to an intermediate level, causing HDAC release and inducing cyclin E expression. By remaining complexed with BRG1/hBRM, Rb continues to repress the expression of cyclin A, a molecule important for S phase, but not G1. Increased cyclinE/cdk2 activity causes additional phosphorylation of Rb as well as BRG1/hBRM, resulting in complete dissociation of this complex from E2F, enabling subsequent expression of cyclin A (195, 196). Concomitantly, the cdk partner is regulated by post-translational modifications. Inhibitory threonine and tyrosine phosphorylations are relieved by cdc25 phosphatases and by phosphorylation of a pivotal threonine residue by cdk activating kinase (CAK) (197, 198, 199). All of these events direct normal cells through G1 and S in a regulated fashion in response to cell activation signals.

5.3. Cyclins, kinases, and inhibitors

Tax impacts the careful regulation of cell cycle progression at multiple points including upregulating expression of at least two cyclins, cyclin D1 and D2 through NF-kappa B response elements (200). Tax also increases the kinase activity of cdk2, 4, and 6 by increasing their expression (201) as well as enhancing the interaction between cdk4 and cyclin D2 by direct interaction with cdk4 (202). These activities result in increased and earlier phosphorylation of Rb and release of E2F. Rb-directed expression of cyclin E leads to cyclin A expression and entry of Tax-expressing cells into S phase earlier than non-Tax expressing cells (203, 204).

Tax also affects the activity of two families of cdk inhibitory proteins, p16 and p21. The p16 family includes four members, p15INK4b, p16INK4a, p18INK4c, and p19INK4d (205, 206), which function to inactivate cdk4 and cdk6. Tax can bind p16 INK4a and interfere with its ability to inhibit cdk4, thereby enabling cdk4-cyclin D activity and cell cycle progression (207, 208, 209). Similarly Tax also interacts with p15INK4b to inhibit its activity, resulting in active cdk4 (210). Alternatively, Tax has been reported to repress transcription of p18INK4c (211) and to reduce p19INK4d protein levels (201). The p21 family includes three members, p21cip1, p27kip1, and p57kip2 that interact with both cyclin and cdk subunits to form inactive, ternary complexes (206, 212, 213, 214). Tax is known to upregulate transcription of the p21 promoter (201, 215, 216, 217), which should lead to inactivation of cdk-cyclin complexes; however, the p21 protein does not appear to be active at the G1/S checkpoint in Tax-expressing cells (Lemoine and Marriott, unpublished data). Tax also binds cdk4 directly, as mentioned above, resulting in increased cdk4 kinase activity (218). These varied Tax activities may propel the infected

cell, unregulated by normal cellular checkpoints, through G1 phase of cell cycle. Although the story of how Tax exploits and disrupts the cell cycle to promote viral activities is most certainly incomplete, its ability to influence cell cycle progression at multiple points and through multiple interactions stands as a model of the versatility and pleiotropism of viral oncogenes.

6. CONCLUSIONS/PERSPECTIVES

Efficient HTLV-I infection generally occurs by cell-to-cell transmission, a relatively inefficient overall strategy to achieve widespread infection (219, 220, 221). The myriad activities impacted by Tax protein presumably constitute a strategy that promotes viral transmission. Tax both upregulates and downregulates cellular gene expression unconstrained by normal cellular regulatory pathways. It interacts with multiple proteins, including MAD1 or p21, to alter their functional characteristics. The goal of these activities benefit the virus by promoting successful viral replication, host cell proliferation and evasion of immune surveillance, enabling the virus to produce virion progeny and spread infection. The by-product of these activities, however, is a cellular system gone awry. The cumulative results of Tax-mediated disruption of cellular gene expression and regulatory pathways, along with the effects of other HTLV-I proteins, are infected cells poised to advance to a diseased state. The likelihood that HTLV-I infections will continue to increase in number emphasizes the urgency of ongoing and future studies, which will increase our understanding of molecular mechanisms by which Tax and HTLV-I cause disease and provide potential targets for therapeutic interventions in the diseases caused by this virus.

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Send correspondence to: Dr Susan J. Marriott, Assoc. Professor, Dept. Molecular Virology and Microbiology, One Baylor Plaza, Houston, TX 77030, Tel: 713-798-4440, Fax: 713-798-3490, E-mail: susanm@bcm.tmc.edu