Life, Death, and Tax: Role of HTLV-I Oncoprotein in Genetic Instability and Cellular Transformation*

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Human T-cell leukemia virus type I (HTLV-I)[1] causes adult T-cell leukemia (ATL) (1–3). The virus is also associated with a neuropathy/myelopathy termed HTLV-associated myelopathy and tropical spastic paraparesis. ATL develops in 2–5% of HTLV-I-infected individuals after a long latent period, suggesting a multistage process of immortalization and transformation of T-lymphocytes. Extant data suggest that 8 discrete events likely occur serially *in vivo* before an HTLV-I-infected cell becomes immortalized and transformed (4). How HTLV-I infection progresses from clinical latency to T-cell malignancy is not well understood but involves the unique viral transactivator/oncoprotein, Tax (Fig. 1). Tax has been shown to be singly sufficient for immortalizing T-lymphocytes (5, 6) and transforming rat fibroblasts (7). Further, transgenic mice expressing Tax (driven by the HTLV-I long terminal repeat (LTR)) develop neurofibroma, a tumor of mesenchymal tissue (8). Finally, large granular lymphocytic leukemia has been found in mice transgenic for Tax expressed from the T-cell specific, granzyme B promoter (9).

It is estimated that cells in the human body divide 10^{16} times during a lifetime. To control and prevent errors in cell divisions, mammalian cells have evolved "gatekeepers" and "caretakers" to regulate the rate of cell growth and the fidelity by which cellular genetic information is transmitted to progenies (10). Gatekeepers monitor the net proliferative capacity of a cell, whereas caretakers act to eliminate DNA damages. Accordingly, one perspective is that transformation occurs when both gatekeeper and caretaker functions are abrogated. Using HTLV-I as a model, we review in a non-exhaustive fashion current thoughts on how Tax perturbs normal cellular regulation and engenders cellular transformation.

The Molecular Biology of HTLV-I

HTLV-I belongs to the *Deltaretrovirus* genera of the Orthoretrovirinae family. *In vivo*, the virus has a tropism for CD4+ T-cells (11) although CD8+ T-cells may also serve as a reservoir (12). HTLV-I infection is primarily transmitted via cell-cell contact (13, 14). Recently, the human Glut1 glucose transporter has been identified as a receptor for infection by cell-free virus (15). The proviral genome of HTLV-I is roughly 9 kbp, and like other retroviruses, contains two LTRs flanking structural genes encoding Gag, Pol, and Env (Fig. 1). An additional region located between *env* and the 3′-LTR, known as the pX region, encodes accessory proteins. The pX region has four partially overlapping reading frames (ORF, Fig. 1), of which ORF IV encodes Tax.

Tax is predominantly a nuclear phosphoprotein (16), which can shuttle into the cytoplasm using a nuclear export signal (17). The mechanism of this shuttling is unclear; however, recent findings that Tax binds tristetrapolin (18) and that tristetrapolin associates with nucleoporin Nup214 (19) raise the possibility that tristetrapolin may serve as a possible nucleocytoplasmic transporter for Tax. Nevertheless, the primary nuclear activity of Tax is to modulate transcription from the HTLV-I LTR (20–22) and cellular promoters including those for IL-2, IL-13, IL-15, IL-2R, c-Fos, and granulocyte macrophage colony-stimulating factor (23–30) among others. Indeed the breadth of Tax's transcriptional reprogramming of host cell genes was verified by DNA array studies which showed that of 2000 assayed genes the expression profiles of ∼300 were significantly altered (31). Tax influences so many promoters through its capacity to act in four discrete signaling pathways: CREB/ATF (reviewed in Ref. 32); NF-κB (reviewed in Ref. 33); AP-1 (34); and SRF (35). These Tax signaling cascades are discussed in greater detail elsewhere (36).

Tax and Cell Cycle Progression

In the course of transforming cells, viral oncoproteins such as E1A, HPV E7, and SV40 T Ag profoundly dysregulate cell cycle controls (37–39). Transition from one phase of the cell cycle to the next is normally governed by cyclin-dependent kinases (CDKs) partnered with cyclins. These CDK-cyclin complexes are in turn modulated by phosphorylation mediated through CDK-activating kinases and phosphatases, and through physical sequestration by CDK inhibitory proteins (reviewed in Refs. 40 and 41).
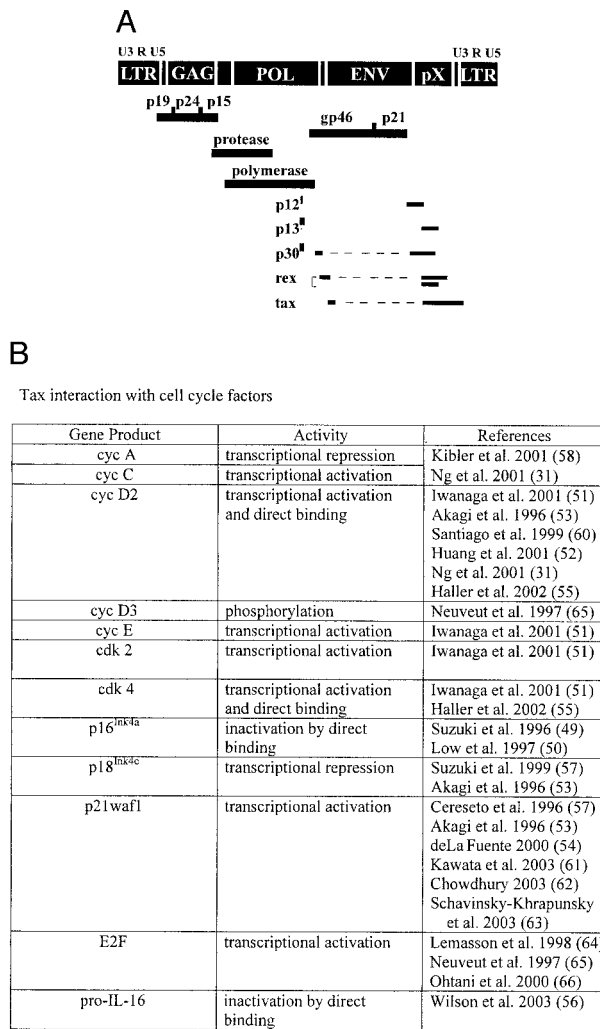
An important cell cycle control resides at the transition from G_1 to S, which is substantially governed by the retinoblastoma tumor suppressor (Rb) (42, 43). At this juncture, D- and E-cyclins with partner CDKs (reviewed in Refs. 40, 41, and 44) converge to phosphorylate Rb. Hypophosphorylated Rb sequesters and inactivates E2F factors, which are needed for the expression of genes (such as dihydrofolate reductase, DNA polymerase α, and cyclins) that are critical for S phase events (reviewed in Ref. 45). Hyperphosphorylated Rb releases E2F, activates E2F-responsive genes, and secures the passage of cells from G_1 into S (45–48). Thus, regulation of Rb phosphorylation by cyclin-Cdk and CDK inhibitory proteins such as $p16^{INK4a}$, $p21^{CIP1/WAF1}$, and $p27^{Kip1}$ is a critical mechanism for influencing gatekeeper function (37).

Tax reprograms G_1 to S progression through multiple mechanistic ways (*i.e.* direct protein-protein binding, transcriptional induction/repression, and post-translational modification such as phosphorylation). Fig. 1*B* summarizes several key cell cycle factors that have been experimentally shown to be influenced by Tax. For instance, Tax can directly bind $p16^{INK4a}$, CycD2, pro-IL-16, and Cdk4 (49–56). On the other hand, $p18^{INK4c}$ (53, 57), CycA (58), CycC (31), CycD2 (31, 51–55, 60), CycE (51), Cdk2 (51), $p21^{CIP1/WAF1}$ (53, 54, 59–63), and E2F (64–66) are regulated by Tax via transcriptional induction/repression (see Fig. 1*B*). Finally, Tax via an unknown mechanism influences the phosphorylation of CycD3 (65). To properly consider this complex pattern of interactions, one should appreciate that the context of Tax's up- or down-regulation matters. An instructive example is presented by Tax-$p21^{CIP1/WAF1}$ interaction. Various studies agree that $p21^{CIP1/WAF1}$ levels are significantly elevated in Tax-expressing cells (53, 54, 61–63). However, depending on whether $p21^{CIP1/WAF1}$ complexes with CycD/Cdk2 or CycA/Cdk2, it has been noted that the resulting ternary complex either promotes or inhibits G_1/S progression (67–69). These observations, if correct, help to explain seemingly opposing effects of Tax on CycD (up-regulated (31, 51–55)) and CycA (down-regulated (58)) transcription. Indeed, enhanced transcription of CycD in the face of repressed transcription of

[1] The abbreviations used are: HTLV-I, human T-cell leukemia virus type I; ATL, adult T-cell leukemia; LTR, long terminal repeat; IL, interleukin; CDK, cyclin-dependent kinase; BER, base excision repair; NER, nucleotide excision repair; PCNA, proliferating cell nuclear antigen; MSC, mitotic spindle assembly checkpoint; AML, acute myeloid leukemia.
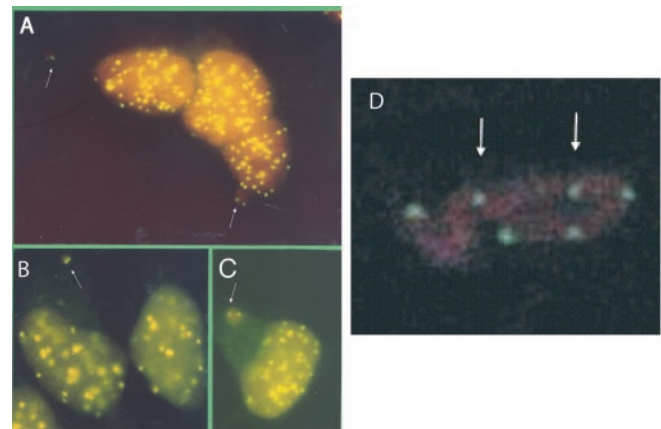
FIG. 2. **Tax causes chromosomal mis-segregation and chromosomal breakage and fusion events.** *A–C*, examples of monkey fibroblast cells that were transfected with Tax and stained 48 h later with propidium iodide and anti-kinetochore antisera. *Arrows* point to small aberrant sacules of DNA, commonly termed micronuclei. Intensely stained dots within micronuclei indicate the presence of kinetochores, which reflect inappropriate segregation of centromere-containing chromosomes. *D*, an example of a chromosome from Tax-expressing cells that exhibit multiple breakage and fusion events. Bright interstitial dots in the chromosome represent *in situ* hybridization with a telomere-specific probe. The six telomere spots indicate that this chimeric chromosome has undergone a minimum of two breakage and fusion events.

All cells acquire DNA damage at a low frequency as they transit the cell cycle. Several mechanisms, including base excision repair (BER), nucleotide excision repair (NER), recombination, and direct repair of nicks by DNA ligation act to correct genetic mistakes. In 1990, the first clue that HTLV-I subverts cellular DNA repair came from the finding that Tax repressed the expression of DNA polymerase β, an enzyme involved in BER (81). Subsequently, reduced BER activity was confirmed in HTLV-I, HTLV-II, and bovine leukemia virus-transformed cells (82). Next, Tax was found to suppress the NER normally observed following UV irradiation of cells (83). NER requires DNA polymerases δ and ϵ and uses proliferating cell nuclear antigen (PCNA) as a cofactor. Excessive PCNA can prompt DNA polymerase δ to synthesize inappropriately new DNA past template lesions, resulting in nucleotide misincorporation (84). Tax is believed to inhibit NER through its transcriptional up-regulation of PCNA (85); this inhibition of NER also depends, in part, on Tax's inactivation of p53 function (71–74).

There is no evidence that Tax interferes with DNA ligation (86) or DNA recombination. However, recent data suggest that Tax represses the expression of human telomerase (hTert) (87). Repression of telomerase is significant because the telomeric repeats of chromosomes normally prevent aberrant end-to-end fusions (Fig. 2*B*) and protect the ends from degradation by exonucleases. Furthermore, *de novo* double-stranded breaks in chromosomes can also be stabilized by the transient addition of telomeric repeats (88–90). Indeed, we have documented that Tax prevents such addition of telomeric repeats to new double-stranded breaks (91) and in this way potentially interferes with a protective mechanism used to prevent inappropriate breakages-fusions (Fig. 2*B*). The combined effects of Tax on BER, NER, DNA end stability, telomerase, and cell cycle progression create a setting in which repair of mistakes is compromised. These combined dysregulations might explain the observed 2.8-fold increase in genomic mutation frequency (92) in HTLV-I-infected cells.

Tax and Aneuploidy

The majority of cancers are aneuploid (93). In transformed cells, numerical chromosomal changes that include losses or gains of entire chromosomes (aneuploidy) generally co-exist with structural chromosomal damage.[2] Although controversial, increasingly aneuploidy is thought to be a cause, rather than a consequence, of transformation (95).

During normal mitosis, human diploid cells maintain euploidy by precisely partitioning 23 pairs of chromosomes from a mother cell to two daughter cells. ATL cells, by contrast, are famously aneuploid (reviewed in Ref. 79). Their nuclei are highly lobulated or

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FIG. 1. **HTLV-I Tax interacts with many cell cycle factors.** *A*, genome organization of HTLV-I with an enlarged presentation of the Tax-encoding pX region. *B*, a tabular summary of some of the cell cycle factors that have been found to interact with Tax.

B Tax interaction with cell cycle factors

Gene Product	Activity	References
cyc A	transcriptional repression	Kibler et al. 2001 (58)
cyc C	transcriptional activation	Ng et al. 2001 (31)
cyc D2	transcriptional activation and direct binding	Iwanaga et al. 2001 (51) Akagi et al. 1996 (53) Santiago et al. 1999 (60) Huang et al. 2001 (52) Ng et al. 2001 (31) Haller et al. 2002 (55)
cyc D3	phosphorylation	Neuveut et al. 1997 (65)
cyc E	transcriptional activation	Iwanaga et al. 2001 (51)
cdk 2	transcriptional activation	Iwanaga et al. 2001 (51)
cdk 4	transcriptional activation and direct binding	Iwanaga et al. 2001 (51) Haller et al. 2002 (55)
p16^{Ink4a}	inactivation by direct binding	Suzuki et al. 1996 (49) Low et al. 1997 (50)
p18^{Ink4c}	transcriptional repression	Suzuki et al. 1999 (57) Akagi et al. 1996 (53)
p21waf1	transcriptional activation	Cereseto et al. 1996 (57) Akagi et al. 1996 (53) deLa Fuente 2000 (54) Kawata et al. 2003 (61) Chowdhury 2003 (62) Schavinsky-Khrapunsky et al. 2003 (63)
E2F	transcriptional activation	Lemasson et al. 1998 (64) Neuveut et al. 1997 (65) Ohtani et al. 2000 (66)
pro-IL-16	inactivation by direct binding	Wilson et al. 2003 (56)

CycA would tip the balance toward more G_1/S transition-promoting p21$^{CIP1/WAF1}$/CycD/Cdk2 at the expense of G_1/S transition-inhibiting p21$^{CIP1/WAF1}$/CycA/Cdk2 moieties. To date, collective evidence do support that Tax has evolved diverse means to defuse various cellular brakes that guard against accelerated G_1/S progression.

The ability of Tax to shorten the length of G_1 and to accelerate cells into S (70) embodies a constitutive (*i.e.* DNA damage-independent) and a DNA damage-induced component. Thus, direct Tax binding of Cdk4 and its enhancement of CycD-Cdk4 activity (55) occur constitutively and are independent of any DNA damage-triggered events. At the same time, Tax can also subvert DNA damage-induced G_1 arrest enforced through p53 (71–74) (see more below). Currently, how Tax affects other phases of the cell cycle is less clear. Emerging findings suggest that this viral oncoprotein can also impair the DNA damage-induced checkpoint in G_2/M transition (75, 76).

Tax and Structurally Damaged Chromosomes

Cancer is a genetic disease. It is estimated that cancer cells can contain more than 100,000 discrete mutations (77). All cancers can be broadly divided into two groups (reviewed in Ref. 78): those arising from loss of DNA repair function (and therefore have structurally damaged chromosomes) and those with chromosomal instability (and therefore have polypoidy and/or aneuploidy). Clastogenic DNA damage is frequently found in HTLV-I-transformed cells (79) and cells transfected to express Tax (80) (Fig. 2*A*). Clastogenic changes (point mutations, deletions, substitutions, translocations) arise and persist when defects in DNA repair mechanisms co-exist in a cell with a loss in checkpoint functions that would normally eliminate damaged DNA.

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[2] F. Mitelman, B. Johansson, and F. Mertens, personal communication.

convoluted, earning them the name of "flower" cells. This suggests that a cellular mechanism that guards against chromosomal missegregation in mitosis is also subverted by HTLV-I. The mitotic spindle assembly checkpoint (MSC) (96) is a key guardian of euploidy. Interestingly, when several ATL cell lines were tested *ex vivo*, all were found to be deficient in MSC function (97). A potential explanation for this loss arises from two findings: (*a*) Tax binds human Mad1 (98, 99) and (*b*) Mad1 is an integral constituent of the MSC (96). That impairment of Mad1 function by Tax may contribute to ATL pathogenesis finds intriguing support in the clinical courses of non-HTLV-I acute myeloid leukemia (AML). In two large AML series (1213 and 1612 patients, respectively), loss of a single chromosome 7 (note that the gene for human Mad1 maps to chromosome 7 (100)) prognosticated an extremely poor outcome (101, 102). In these two studies, whereas all AML patients had 5-year overall survival rates of 24–44%, counterpart AML patients with monosomy 7 had survival rates of 0–10%, respectively (101, 102). Other explanations not excluded, a tantalizing parallel between the two leukemias is that one (ATL) impairs Mad1 function through viral oncoprotein subversion whereas the other (AML) does so through physical loss of chromosome 7 (*i.e.* monosomy 7).

Is loss of MSC the sole reason for aneuploidy in ATL cells? The answer appears to be "no." Conceptually, one recognizes that loss of checkpoint can explain the tolerance of mistakes by cells, but checkpoint loss cannot create *de novo* mistakes. Recent studies suggest that Tax might directly trigger chromosomal separation errors in two ways. First, Tax can promote the unscheduled degradation of securin and cyclin B1 most likely through the premature activation of the CDC20-associated anaphase promoting complex (103), thereby leading to faulty mitosis. Second, like the human papilloma virus E7 oncoprotein (38), Tax can also induce aberrant centrosomal multiplication in G_1.[3] Generating supernumerary centrosomes results in multipolar mitosis, which is another mechanism for creating aneuploidy (104).

Finally, there is a school of thought that suggests polyploidy as the precursor of aneuploidy (104). Relevant to this notion, we note that Tax expression does facilely create multinucleated (*i.e.* polyploid) cells (76, 98). Add to this the fact that Tax can inactivate p53 and Rb (65, 71–74), two factors essential to a G_1 tetraploid/polypoid checkpoint (105), and one then can further envision how this might be yet another route traveled by HTLV-I/Tax/ATL cells toward aneuploidy (Fig. 3).

Proliferation versus Apoptosis

A long standing cancer paradox is that overexpression of oncogenes does not simply provide proliferative advantages to cells but frequently also triggers cells to undergo apoptosis. Findings from oncogenic transcription factors such as Myc, E1A, and E2F-1 show this duality to be the rule rather than the exception (reviewed in Ref. 106). Indeed, it is now apparent that oncogenic insults induce countervailing responses by the cell, which are reflected in cell cycle arrest and apoptosis. We reviewed, above, how Tax defeats cellular mechanisms for braking cell cycle progression. No cell cycle and/or genetic instability manifestations of Tax can confer selective growth advantage if cells fail to tolerate such phenotypic and genotypic changes and choose instead apoptotic death. Hence, disabling the cellular apoptotic response remains a requisite for transformation.

By definition, the clinical presentation of ATL implies that in a subpopulation of CD4+ T-cells, HTLV-I infection tips the balance between proliferation and apoptosis toward the former. Nevertheless, how HTLV-I Tax oncoprotein influences this choice is not fully understood. Many have examined the contribution of Tax to stress-induced apoptosis. Overall findings have been controversial and divergent. Some found that Tax protects cells from stress-induced cell cycle arrest or apoptosis (107–109), whereas others observed that Tax sensitizes cells to stress-induced apoptosis (110–113). Likely, the decision between proliferation and death is influenced by the cellular environment, cell type genetic background, and multiple co-existing signaling events. Depending on context, which set of genes that Tax transcriptionally activates (31) and/or which cluster of gene products that Tax binds (94) will mean either the normal cellular response against oncogenic stress will either prevail (*i.e.* apoptosis) or be sub-
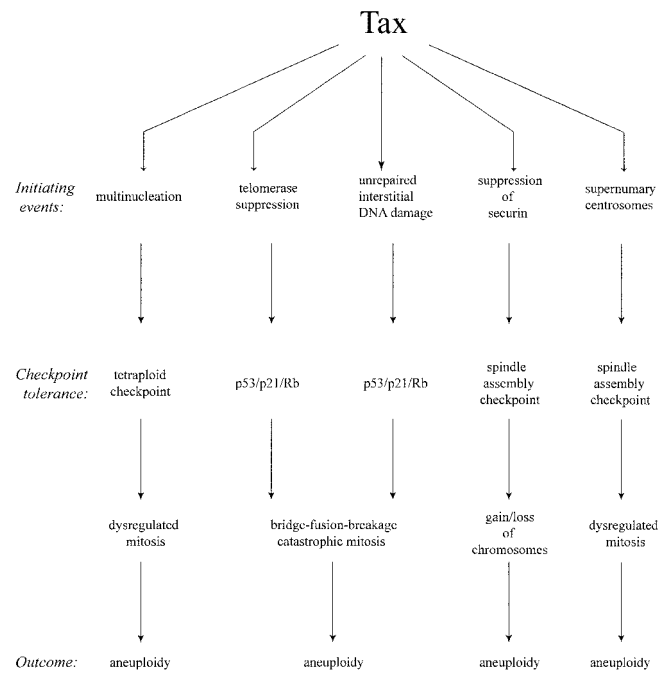
Fig. 3. **A flow diagram of the various routes that Tax could use to generate aneuploidy in cells.** It is emphasized that two discrete events, a damage-initiating stimulus plus the loss of a checkpoint, are required for genetic mistakes to become fixated into the genome.

verted (*i.e.* proliferation) by HTLV-I. A clear understanding of factors in addition to Tax that guide this choice for HTLV-I-infected T-cells will be a major topic for future research.

Concluding Comments

Over 20 million individuals globally are infected with HTLV-I. It is estimated that 2–5% of these carriers will develop ATL over their lifetime. The identification and isolation of HTLV-I 25 years ago have spurred intensive mechanistic investigations into ATL transformation. Using Tax as a model system, we have learned that viral means for transformation parallel similar mechanistic changes seen in spontaneously occurring cancers. A simplified sequence of events appears to be genetic damage initiated by oncogenic stimuli, followed by subversion of cellular checks allowing tolerance and fixation of changes into the genome, and finally selection over time for the correct mix of gene alterations that confer selective growth advantage. Clearly the process is complex and multifaceted. Fleshing out all the biological and molecular details to accompany this simplified framework will easily keep HTLV researchers busy for another 25 years.

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