HTLV-1 and Leukemogenesis: Virus–Cell Interactions in the Development of Adult T-Cell Leukemia

Linda Zane and Kuan-Teh Jeang

Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1) was originally discovered in the early 1980s. It is the first retrovirus to be unambiguously linked causally to a human cancer. HTLV-1 currently infects approximately 20 million people worldwide. In this chapter, we review progress made over the last 30 years in our understanding of HTLV-1 infection, replication, gene expression, and cellular transformation.

Contents

L. Zane · K.-T. Jeang (✉)
Molecular Virology Section, Laboratory of Molecular Microbiology, The National Institutes of Allergy and Infectious Diseases, The National Institutes of Health, Bethesda, MD 20892-0460, USA
e-mail: KJEANG@nih.gov

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1 Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is the first identified human retrovirus. This virus belongs to the Deltaretrovirus genera of the Orthoretrovirinae subfamily which includes HTLV-2, HTLV-3, HTLV-4 (Mahieux and Gessain 2005; Mahieux and Gessain 2009), Bovine Leukemia Virus (BLV), and Simian T-cell lymphotropic virus (STLV). The virus was discovered in 1980–1981 by analyzing T cells from a patient suffering T-cell leukemias (ATL) (Poiesz et al. 1980; Hinuma et al. 1981; Miyoshi et al. 1981; Yoshida 1982; Watanabe et al. 1983; Gallo 2005). ATL is a rapidly fatal disease first described in Japan (Takatsuki 2005). Since then, a causal association between HTLV-1 and ATL has become firmly established (Gallo 2005). To date, HTLV-1 is the only known retrovirus that is directly linked to a human cancer. In addition to this cancer link, the virus can also cause inflammatory diseases such as HTLV-1-associated Myelopathy (HAM)/tropical spastic paraparesis (TSP), uveitis, infective dermatitis, and myositis (Gessain 2011; Goncalves et al. 2010).

2 HTLV-1 Infection

2.1 Epidemiology

Approximately 20 million people worldwide are infected with HTLV-1 (Proietti et al. 2005). However, HTLV-1 is not evenly distributed throughout the world. Indeed, the areas of highest prevalence of HTLV-1 are mainly southern Japan, the Caribbean islands, parts of South America and Central Africa, with foci in the Middle East, and Australia (Goncalves et al. 2010). This geographic distribution of HTLV-1 with some clustering of regions with high prevalence is still not understood (Proietti et al. 2005). Among HTLV-1-infected people, 2–5 % will develop ATL after a long latency period of 30–60-year post-infection; by comparison, approximately 0.25–5 % of the infected individuals will develop HAM/TSP. The development of ATL or TSP/HAM is not influenced by the subtype of HTLV-1 infection (Watanabe 2011; Ono et al. 1994). Indeed, while six subtypes of HTLV-1 (subtypes A-F) have been reported, the great majority of infections are caused by the cosmopolitan subtype A.

HTLV-1 has 3 modes of transmission: (1) mother to child, mainly through prolonged breastfeeding (>6 months); sexual, (2) mainly but not exclusively occurring from male to female; and (3) by blood products contaminated with infected lymphocytes (Goncalves et al. 2010; Matsuura et al. 2010). Male individuals and those infected in their early childhood are at the highest risk of developing ATL (Goncalves et al. 2010; Matsuura et al. 2010).

2.2 Tropism and Receptors

In vitro, HTLV-1 can infect many cell types including several non-lymphoid tumor cell lines such as human osteogenic sarcoma cells, lung cells, cervical carcinoma cells (HeLa), human gastric HGC-27 cells, human promyelocytic leukemia HL60 cells, as well as primary endothelial cells, monocytes, microglial cells, and mammary epithelial cells (Clapham et al. 1983; Hayami et al. 1984; Ho et al. 1984; Hiramatsu et al. 1986; Akagi et al. 1988; LeVasseur et al. 1998). However, in vivo, HTLV-1 is found primarily in CD4+ and CD8+ T lymphocytes (Nagai et al. 2001) and less frequently in other cell types such as monocytes, endothelial cells, myeloid, and plasmacytoid dendritic cells (Macatonia et al. 1992; Koyanagi et al. 1993; Jones et al. 2008), and CD34+ hematopoietic progenitor cells (Banerjee et al. 2008, 2010; Feuer et al. 1996; Grant et al. 2002; Tripp et al. 2003, 2005). Until the discovery of the glucose transporter GLUT1 as a receptor for HTLV-1 in 2003, little was known about the entry receptors for HTLV-1 (Manel et al. 2003). Currently, the published data from different laboratories support the idea of a multireceptor model for HTLV-1 entry (Fig. 1). Three cell surface proteins have been found to be involved in HTLV-1 entry: glucose transporter 1 (GLUT1), neuropilin-1 (NRP-1), and heparan sulfate proteoglycans (HSPG) (Jones et al. 2011). The following steps possibly explain HTLV-1 entry into cells. First, the surface subunit (SU) of the virally encoded envelope glycoprotein interacts with the heparan sulfate proteoglycans/neuropilin-1 complexes. Next, these interactions trigger conformational changes of the SU which are followed by the binding of the SU to GLUT1, and finally membrane fusion occur to allow the entry of the virus into the target cell (Jones et al. 2005, 2011; Pinon et al. 2003; Ghez et al. 2006; Lambert et al. 2009).

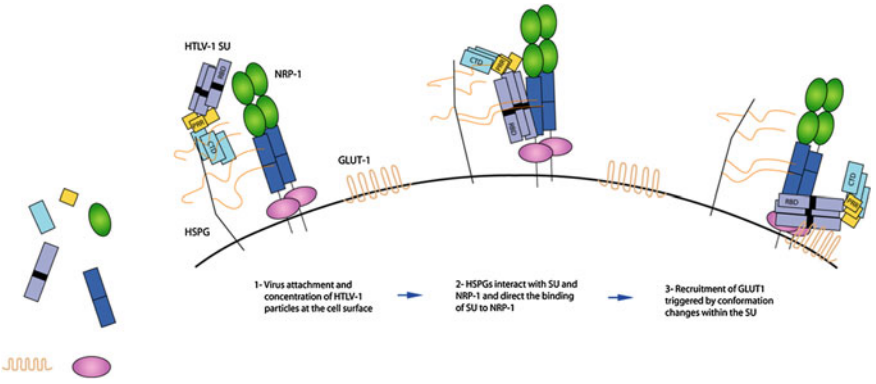

Fig. 1 A multireceptor model for HTLV-1 entry. *HSPG* = heparan sulfate proteoglycans; *SU* = the subunit of HTLV-1 envelope glycoprotein; *NRP-1* = neuropilin-1; *GLUT-1* = glucose transporter 1; *CTD* = C-terminal domain; *RBD* = receptor-binding domain; *PRR* = proline-rich region. This drawing is modified after Jones et al. (2012) (Jones et al. 2011)

2.3 Viral Replication

At the cellular level, HTLV-1 is transmitted via two major routes: through cell-to-cell contact (horizontal transmission) and via clonal expansion of HTLV-1-infected cells (vertical transmission).

2.3.1 Cell-to-Cell Transmission

Naturally infected T lymphocytes produce little to no free viral particles, and the infectivity of these cell-free particles is very low. In vivo, HTLV-1 intercellular transmission, *i.e.,* horizontal, reverse-transcription-based replication, requires close cell-to-cell contact. To date, three mechanisms have been reported in the literature (Fig. 2). First, in 2003, Igakura et al. showed the formation of a "virological synapse," composed of viral and cellular molecules, at the point of contact between the HTLV-1-infected and recipient target cells (Igakura et al. 2003; Nejmeddine et al. 2005). Second, Pais-Correia et al. described that after viral budding, HTLV-1 virions are retained on the cell surface of infected cells in extracellular viral assemblies composed of collagen, agrin, and linker proteins

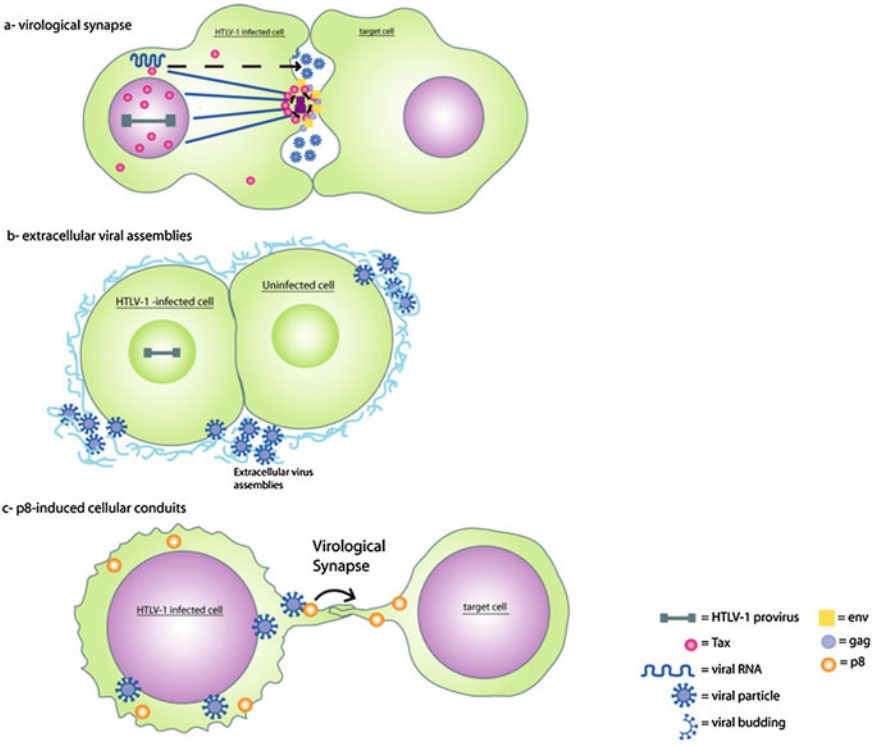

Fig. 2 Mechanisms of cell-to-cell transmission of HTLV-1. This drawing is modified after Yasunaga and Matsuoka (2011)

such as tetherin and galectin-3 (Pais-Correia et al. 2010). When HTLV-1-infected cells attach to uninfected cells, the viral particles contained in these extracellular biofilm-like structures are rapidly transferred to the surface of the target cells, resulting in infection (Pais-Correia et al. 2010). Third, it was recently demonstrated by Franchini and colleagues that HTLV-1 encodes a protein, $p12^{I}$, in its pX region. The processing of $p12^{I}$ generates $p8^{I}$. This protein increases T-cell contact by clustering lymphocyte function-associated antigen-1 (LFA-1); it promotes T-cell conjugation through LFA-1 and intercellular adhesion molecule 1 (ICAM-1) interaction; and it enhances HTLV-1 cell-to-cell transmission by inducing the formation of cellular conduits (Van Prooyen et al. 2010; Fukumoto et al. 2009).

2.3.2 Clonal Expansion

HTLV-1 infection is associated with an elevated proviral load, very low cell-to-cell transmission rate, and high viral genetic stability. This high genetic stability of HTLV-1 (and other deltaretroviruses) is due to its replication in vivo via "the clonal expansion of infected cells" (Wattel et al. 1995; Cavrois et al. 1996; Cavrois et al. 1996; Wattel et al. 1996; Zane et al. 2009). Indeed, instead of using the error-prone viral RT, the HTLV-1 genome is propagated as an integrated provirus that is replicated during cellular DNA synthesis. Since HTLV-1 mostly integrates randomly into the host genome, sequential analyses of integration sites have verified that the proliferation of HTLV-1-infected cells is clonal and persistent (Etoh et al. 1997; Cavrois et al. 1998). In some animal models [e.g., experimentally infected squirrel monkeys (*Saimiri sciureus*) and sheep with HTLV-1 and BLV, respectively], it has been shown that deltaretrovirus infection is a two-step process that includes an early (primo-infection) and transient phase of reverse transcription, before the establishment of an immune response, followed by the persistent multiplication of infected cells by clonal expansion (Mortreux et al. 2001; Pomier et al. 2008). The clonal cells survive over time, and it has been found that ATL originates from one of these clones present during the primo-infection (Moules et al. 2005).

2.4 Viral Expression

As shown in Fig. 3, the HTLV-1 proviral genome contains retroviral structural and non-structural genes. The viral *gag*, *pro*, *pol*, and *env* genes are flanked by the long terminal repeats (LTR) at both ends, and a region named pX is located between *env* and the 3′ LTR. The 5′ LTR serves as the viral promoter for transcription. The Pol open reading frame encodes reverse transcriptase, protease, and integrase. Gag provides the virion core proteins, and Env is used for viral infectivity. The pX region contains four partially overlapping open reading frames (ORFs); and through the use of alternative splicing and internal initiation codons, it encodes several regulatory proteins. Orf-I produces the $p12^{I}$ protein which can be proteolytically cleaved at the amino terminus to generate the $p8^{I}$ protein, while differential splicing of mRNAs from orf-II results in the production of the $p13^{II}$ and

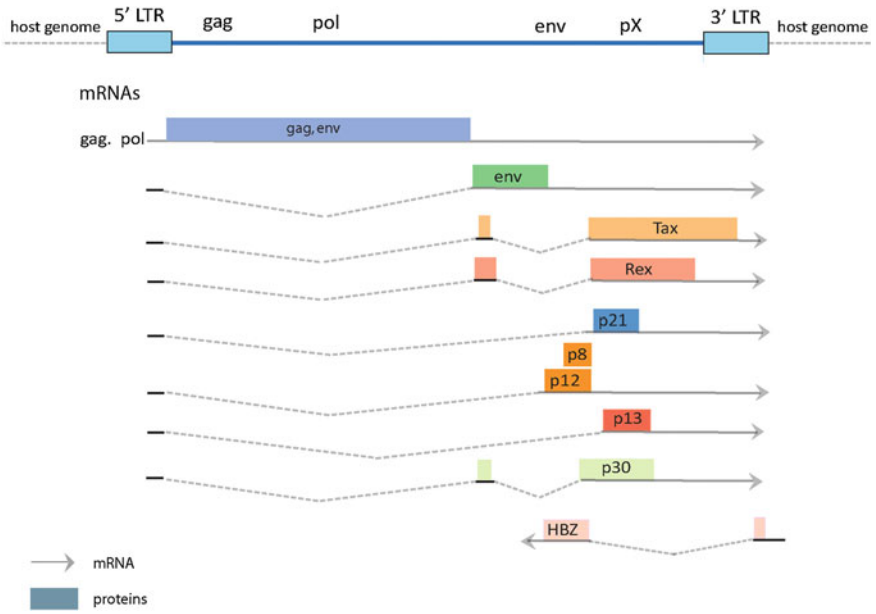

Fig. 3 The HTLV-1 proviral genome showing the expression of various spliced transcripts and the open reading frames (ORFs) that they encode. This drawing is modified from Matsuoka and Jeang (2007)

$p30^{II}$ proteins. Orf-III and orf-IV encode the Rex and Tax proteins, respectively; and an antisense mRNA transcribed from the 3′ LTR generates the HTLV-1 basic leucine zipper (HBZ) protein. Below, we will discuss in brief the roles of Tax and HBZ on the induction and the maintenance of leukemogenesis, respectively (Matsuoka and Jeang 2007).

3 Tax Expression Dictates the Fate of HTLV-1-infected Cells

Expression of the viral Tax oncoprotein is sufficient to immortalize T cells (Grassmann et al. 1992), transform rodent cells (Tanaka et al. 1990), and induce tumorigenesis in mouse models (Hinrichs et al. 1987; Nerenberg et al. 1987; Green et al. 1989; Iwakura et al. 1991; Kwon et al. 2005; Hasegawa et al. 2006; Fu et al. 2011). Recently, Banerjee et al. have reported on the transformation of human cells into leukemic cells. Using immune-deficient NOD/SCID mice, they showed that CD4+ lymphomas can arise from mice that are injected with CD34+hematopoietic progenitor stem cells transduced to express Tax (Banerjee et al. 2010). These data raise the notion that a target of Tax transformation may be the CD34+ hematopoietic progenitor stem cells, instead of and perhaps in addition to the currently considered mature CD4+ or CD8+ T lymphocytes.

To become tumorigenic, cells have to grow more rapidly than non-transformed cells. The tumorigenic cells accumulate genetic changes (clastogenic damage or aneuploidy) and enforce the propagation of these aberrant changes by neutralizing the cell cycle checkpoints. To be effective, tumorigenic cells must also evade the host's immune responses (Hanahan and Weinberg 2000, 2011).

Data from multiple laboratories over the past 25 years have begun to shed light on how Tax confers growth advantage to HTLV-1-infected cells, and how this viral oncoprotein triggers DNA damage accumulation and inhibits the cell cycle checkpoints during its transformation of a normal cell into a leukemic cell (Fig. 4).

3.1 Tax Promotes the Survival and the Proliferation of HTLV-1-infected Cells

3.1.1 Tax and Apoptosis and Senescence

Like other oncogenes, Tax confers pro-proliferative and pro-survival properties to cells (Schmitt et al. 1998; Xiao et al. 2001; Iwanaga et al. 2008). Curiously, its expression also has been reported to trigger apoptosis (Yamada et al. 1994; Chlichlia et al. 1995; Fujita and Shiku 1995; Chen et al. 1997; Hall et al. 1998; Kao et al. 2000; Nicot and Harrod 2000) and senescence (Kinjo et al. 2010; Yang et al. 2011; Zhi et al. 2011). These apparently contradictory findings are reconciled if one realizes that Tax performs a single signaling event that differentially elicits either a growth or death/senescence response depending on the context of the cell. Thus, the Tax signal for cells to grow capably stimulates cellular to proliferation under physiologically conditions favorable for growth conditions. On the other hand, under austere conditions that are non-permissive for cellular growth, the same Tax proliferative signal presumably attempts to initiate an increased metabolic program that cannot be consummated and instead the cells react by committing apoptosis or entering senescence (Kasai and Jeang 2004). Stated another way, Tax signaling is always intended to promote cell division. Cells, depending on context, can respond to that dictate to proliferate by growing or by executing apoptosis/senescence. Thus, Tax does not have two countervailing and contradictory functions; rather, it is the same function that elicits two different cellular outcomes (proliferation *versus* apoptosis/senescence) depending on the status of the infected cell (Jeang 2010; Boxus and Willems 2012). In vivo, because HTLV-1 infection ultimately leads to leukemogenesis and T-cell proliferation in some individuals, in these persons, it is clear that the prevailing effect of Tax is pro-proliferative and anti-apoptotic (Copeland et al. 1994; Kishi et al. 1997; Arai et al. 1998; Mulloy et al. 1998; Kawakami et al. 1999); in others who do not develop ATL, it is possible that apoptotic/senescent cellular responses predominate. For understanding the process of leukemogenesis, Tax's activity on factors such as p53 (Mulloy et al. 1998; Haoudi and Semmes 2003; Jung et al. 2008) and NF-kB is

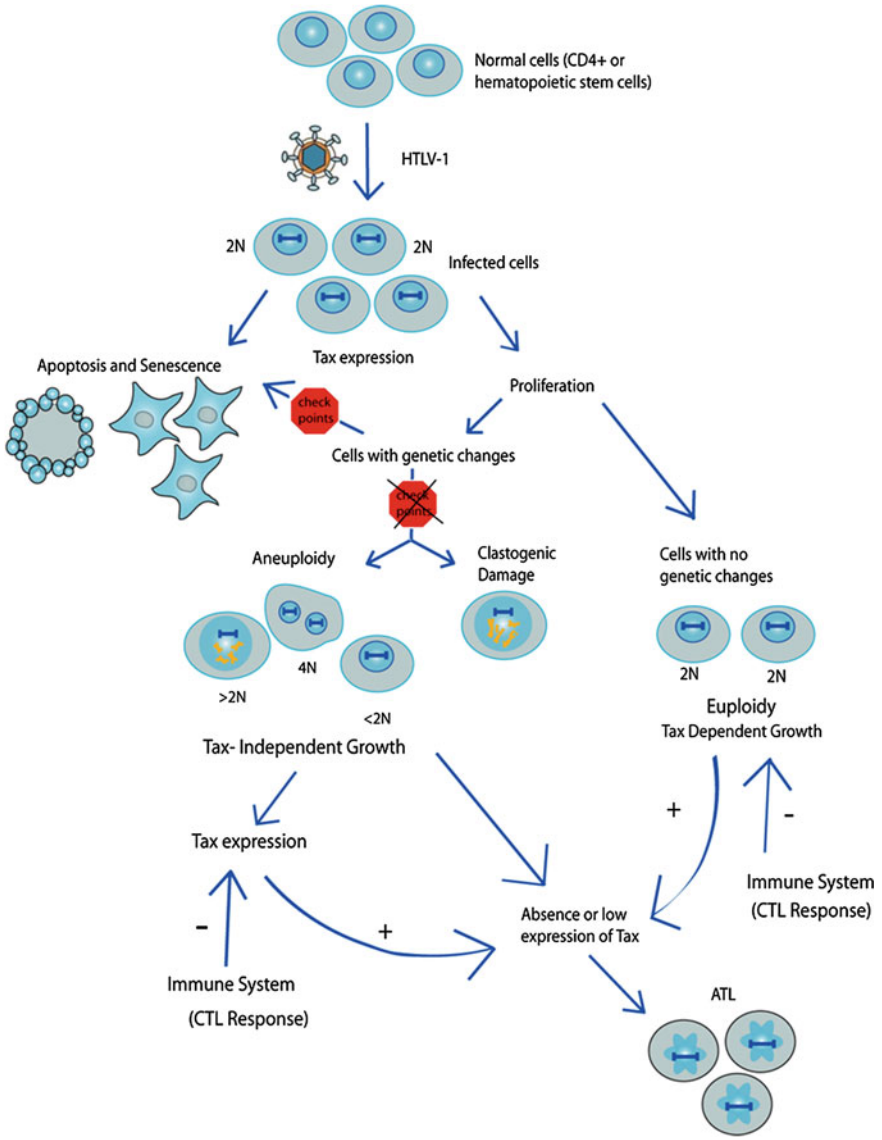

Fig. 4 Multistep processes that lead to the transformation of normal hematopoietic cells into ATL cells. The scheme incorporates the concept that ATL leukemogenesis is induced by Tax. This drawing is modified from Matsuoka and Jeang (2011)

consistent with the requirements in transformed cells of activating anti-apoptotic genes and suppressing pro-apoptotic genes (Kawakami et al. 1999; Tsukahara et al. 1999; Nicot et al. 2000; Mori et al. 2001; Pise-Masison et al. 2002; Krueger et al. 2006; Okamoto et al. 2006; Waldele et al. 2006).

3.1.2 Tax and NF-κB

NF-κB is a major survival factor engaged by HTLV-1. NF-κB is constitutively active in most tumor cells, and its suppression inhibits the growth of tumor (Chaturvedi et al. 2011; Perkins 2012). Although tightly controlled in normal cells, including T cells, NF-κB is constitutively activated in both transformed and untransformed HTLV-1-infected cells (Watanabe et al. 2005; Qu and Xiao 2011).

The NF-κB family of transcription factors has five closely related DNA-binding proteins (RelA (p65), RelB, c-Rel, NF-κB1/p50, and NF-κB2/p52) that can form various homodimers and heterodimers to regulate the transcription of genes containing κB motifs in their promoters. Latent or unstimulated cells sequester NF-κB dimers in the cytoplasm using inhibitors of kappa B (IκBs) proteins such as IκBα and p100. Upon activation, IκBs are degraded (canonical pathway) or p100 is processed to generate p52 (non-canonical pathway) leading to the translocation of active NF-κB proteins into the nucleus to activate transcription (Qu and Xiao 2011; Rauch and Ratner 2011). In the canonical pathway, IκBα degradation requires its phosphorylation by a specific IκB kinase (IKK) complex composed of two catalytic subunits IKKα (or IKK1) and IKKβ (or IKK2), and a regulatory subunit IKKγ (or NEMO). This phosphorylation results in rapid ubiquitination and proteasomal degradation of IκBα, allowing RelA (or p65), and other NF-κB members to localize to the nucleus in order to induce gene expression. In the non-canonical NF-κB pathway, IKKγ is specifically recruited into the p100 complex to phosphorylate p100, leading to p100 ubiquitination and processing to p52 which then associates with NF-κB-binding partners and translocates into the nucleus to induce or repress gene expression (Qu and Xiao 2011).

Work from many investigators has shown that Tax activates both canonical and non-canonical NF-κB signaling pathways in HTLV-1-infected cells (Xiao et al. 2001; Iha et al. 2003; Qu and Xiao 2011). Tax persistently activates IKK through binding to IKKγ, leading to the degradation of IκBα (canonical pathway) (Chu et al. 1999; Harhaj and Sun 1999; Jin et al. 1999; Xiao et al. 2000); and Tax promotes the formation of an IKKα-IKKγ-p100 complex followed by the processing of the NF-κB p100 precursor protein to its active p52 form (non-canonical pathway) (Xiao et al. 2001). Tax also binds to and increases the stability and activity of NF-κB (Hirai et al. 1992; Suzuki et al. 1993; Suzuki et al. 1994) and inactivates NF-κB inhibitors (Maggirwar et al. 1995; Suzuki et al. 1995; Good and Sun 1996; McKinsey et al. 1996; Petropoulos et al. 1996).

Recently, two independent studies using two different Tax transgenic mouse models have revealed that Tax-induced tumorigenesis is dependent on the NF-κB pathway and that both canonical and non-canonical NF-κB pathways are involved in this process (Kwon et al. 2005; Fu et al. 2011). The first study used mice expressing a wild-type Tax or a mutant form of Tax that is unable to activate the NF-κB pathway. A lethal cutaneous disease that shares several features in common with the skin disease that occurs during the preleukemic stage in HTLV-1-infected patients developed in the wild-type Tax–expressing mice (Kwon et al. 2005). In the second study, the investigators found that the genetic knockout of the NF-κB2

gene alone dramatically delayed tumor onset in Tax-expressing transgenic mice (Fu et al. 2011).

3.1.3 Tax and the Cell Cycle

Progression through the cell cycle is a tightly controlled process regulated by interactions between cyclins and cyclin-dependent kinases (CDKs). Tax deregulates the progression of infected cells through different phases of the cell cycle, especially the progression through G1.

Tax propels the cell through G1 by increasing the formation of complexes of cyclin D/CDK4, cyclin D/CDK6, and cyclin E/CDK6 via several mechanisms (Marriott and Semmes 2005). First, Tax can transcriptionally activate the expression of cyclins D2 (Akagi et al. 1996; Santiago et al. 1999; Iwanaga et al. 2001) and E (Iwanaga et al. 2001), CDK2 and 4 (Iwanaga et al. 2001), and transcriptionally repress CKIs such as $p18^{INK4c}$, $p19^{INK4D}$, and $p27^{KIP1}$ (Suzuki et al. 1999; Iwanaga et al. 2001). Additionally, Tax can directly bind CDK4 (Haller et al. 2002; Fraedrich et al. 2005) and $p16^{INK4a}$, thereby preventing the inhibitory $p16^{INK4a}$ molecule from binding to CDK4 and CDK6 (Low et al. 1997). Finally, Tax directly binds the retinoblastoma (RB) protein, which is a target substrate of cyclin D/CDK4/CDK6 and cyclin E/CDK2 complexes, and triggers proteosomal degradation of the RB protein; this then leads to the release of the E2F1 transcription factor from RB and the transcription of E2F1-responsive genes whose products are necessary for passage of the cells through G1 into S phase (Kehn et al. 2005). Moreover, it has also been reported that Tax expression activates the transcription of the *E2F1* gene (Mori 1997; Lemasson et al. 1998; Ohtani et al. 2000).

Another fundamental property of Tax is that it can inhibit the G1/S checkpoint to allow cell cycle progression to happen even with the presence of DNA damage (Marriott and Semmes 2005). Accordingly, Tax can inhibit p53 activity which functions to monitor DNA structure integrity at the G1/S transition (Tabakin-Fix et al. 2006).

3.2 Tax-Expressing Cells Accumulate DNA Damage

Genetic instability of HTLV-1-infected cells generates the acquisition of eight biological changes predicted to be needed for the multistep development of ATL (Hanahan and Weinberg 2000, 2011). Two major types of genetic instability include the loss of DNA repair capabilities and the loss of euploidy. Indeed, Tax is able to disrupt normal cellular processes of DNA repair and chromosomal segregation (Majone et al. 1993; Saggioro et al. 1994, 1996; Lemoine and Marriott 2002).

3.2.1 Tax and Clastogenic Damage

The chromosomes in ATL cells show clastogenic damage (Marriott et al. 2002). Tax engenders direct DNA damage by increasing reactive oxygen species (Kinjo et al. 2010) and/or by inhibiting p53 checkpoint function (Tabakin-Fix et al. 2006).

Two major mechanisms have been hypothesized to explain Tax-abrogation of p53 function. One model suggests that there is a competition between p53 and Tax for binding to the transcription coactivator CREB–binding protein (CBP)/p300 (Ariumi et al. 2000); a second model suggests that Tax activation of NF-κB is required for its inactivation of p53 (Miyazato et al. 2005). More recent data suggest that neither model satisfactorily explain Tax-p53 functional interaction, leaving incompletely answered the question of how Tax disables p53 function.

3.2.2 Tax and Aneuploidy

The majority of cancer cells including ATL cells are aneuploid. Aneuploidy has been proposed to be a cause of transformation. It has been shown that Tax can induce aneuploidy via several mechanisms. Tax can directly trigger chromosomal separation errors in two ways. First, Tax has been shown to cause multipolar mitosis (Peloponese et al. 2005; Ching et al. 2006; Nitta et al. 2006). Tax can also induce aberrant centrosomal multiplication by targeting the cellular TAX1BP2 protein, which normally blocks centriole over-duplication (Ching 2006). Second, during mitosis, Tax engages RANBP1 and fragments spindle poles, provoking multipolar segregation (Peloponese et al. 2005). Moreover, Tax has also been shown to promote premature mitotic exit by binding and activating the anaphase-promoting complex/cyclosome (APC/C). Finally, Tax-expressing cells are lost for the "aneuploidy" checkpoint in mitosis because of Tax-mediated inactivation of the critical spindle assembly checkpoint protein, Mad1 (Liu et al. 2005; Jin et al. 1998).

4 ATL

4.1 Absence of Tax Expression and Evasion of the Host's Immune Surveillance

HTLV-1 chronic infection arises when an equilibrium is established between viral virulence and the host immunity. HTLV-1 requires Tax expression to transform cells, but Tax is also the main target of the host's cytotoxic T Lymphocytes (CTLs) (Jacobson et al. 1990; Kannagi et al. 1991; Elovaara et al. 1993; Yamano et al. 2002). Thus, biologically, the virus has to evolve a process to control Tax expression to evade the host's immune surveillance. Early after infection, the current view is that Tax is needed to initiate the cascade of events leading to transformation. On the other hand, Tax-expressing cells immediately become recognized as foreign entities and are targeted by the host's immune system (cytotoxic T cells, CTL) for elimination. Accordingly, a balance has to be reached between growth advantage conferred by Tax to the cell and the susceptibility of the same cell to CTL killing. Early in virus infection when growth advantages conferred by Tax outweigh CTL killing, Tax expression is maintained in virus-infected cells; later in infection, the opposite may be the case which then explains

why most HTLV-1 transformed cells become silenced for Tax expression. Thus, it is currently considered that although Tax is needed early to initiate transformation, when cells become transformed, Tax is no longer needed for maintenance of transformation. Given that situation and the need to evade CTL killing, it is not surprising that in ATLs cells late in the course of virus infection, more than 60 % of such cells show no detectable Tax transcripts (Takeda et al. 2004; Taniguchi et al. 2005; Miyazaki et al. 2007). While it is still not fully understood how Tax expression is silence, some of this likely occurs from genetic changes in the Tax gene (Furukawa et al. 2001; Takeda et al. 2004), epigenetic changes in the viral promoter in the 5′LTR (DNA hypermethylation and histone modifications) (Koiwa et al. 2002; Takeda et al. 2004; Taniguchi et al. 2005), and/or deletion of 5′LTR sequences (Tamiya et al. 1996).

4.2 HBZ Expression

The mechanism of how cells acquire Tax-independent proliferation is not completely understood. One explanation is that the genetic host chromosomal changes accumulated over time in HTLV-1-infected cells may have conferred sufficient virus-independent transformation/growth properties to those cells. An additional explanation may be the expression of the viral HBZ transcript/protein. Indeed, HBZ mRNA is highly expressed in ATL cells (Murata et al. 2006; Satou et al. 2006; Miyazaki et al. 2007). Using in vivo models, it has been shown that HBZ is expressed later than Tax in the infected cell, and its expression increases over time (Li et al. 2009). In contrast to Tax, HBZ sequence is not mutated in ATL cells (Fan et al. 2010), and the 3′LTR containing its promoter remains intact (Taniguchi et al. 2005; Fan et al. 2010). Moreover, although HBZ is an immunogenic protein, HBZ-specific CTLs seem unable to efficiently eliminate HTLV-1-infected cells (Suemori et al. 2009). HBZ further promotes virus-infected cell to proliferate late in infection (Satou et al. 2006), and its silencing of viral expression appears to enhance virus-infected cells to escape the host's immune response (Gaudray et al. 2002). The complementary expression patterns of Tax and HBZ suggest that Tax and HBZ may act early and late, respectively, in virus infection with the former used to initiate transformation and the latter utilized to maintain the transformed phenotype of ATL cells.

5 Concluding Remarks

Despite robust progress, several questions regarding ATL leukemogenesis remain unresolved. First, what is the true cellular target of virus/Tax transformation? To date, only human CD34+ hematopoietic progenitor stem cells have been successfully transformed by Tax while other differentiated human primary cells have been refractory to Tax-mediated transformation. Thus, it is unclear what cellular

factor differences between progenitor versus differentiated human cells govern Tax-induced transformation? Second, how does Tax fully inactivate p53 function? As mentioned above, current hypotheses on how Tax inactivates p53 appears to be unsatisfactory. Third, what factors are needed for the initiation of ATL versus those needed for maintenance of ATL? One anticipates that progress will be made on these and other questions in the coming years.

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