Chapter 2
Human T-Cell Leukemia Virus Type 1 (HTLV-1)

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2.1 Human T-Cell Leukemia Virus Type 1 (HTLV-1) as the First Human Retrovirus

Within several decades after identification of the first retroviruses as agents of neoplastic diseases in chickens at the beginning of last century [36, 150], a large number of "RNA tumor virus" were found in fowl, mice, cat, cattle, and monkeys. In addition to the extraordinary and unique features of life cycle such as reverse transcription of genomic RNA to DNA and its integration into the host chromosomal DNA, analysis of retroviruses led to the finding of "oncogenes" and provided a strong evidence for the paradigm, the genetic origin of cancer. However, retroviruses had been searched for without success in most types of human tumors by the end of the 1970s; thus, it seemed questionable whether a human retrovirus existed at all.

In 1980, the first human retrovirus was found in a T-cell line established from a patient with mycosis fungoides, and the retrovirus was named human T-cell leukemia virus type I (HTLV-1) [145], but the link between this retrovirus and human disease was not certain. Prior to this finding, Takatsuki and his colleague reported a new disease entity, adult T-cell leukemia (ATL). Patients with ATL were clustered in a limited area of Japan, including the islands of Kyushu and Okinawa, which suggested a transmissible leukemogenic agent [178]. A large number of T-cell lines, so-called ATL cell lines, were established from ATL patients, and it was found that all ATL patients had antibodies that reacted with these cell lines, confirming the involvement of virus infection [65]. Subsequently, a retrovirus particle was identified in the ATL cell line [127], and the nucleotide sequence of the retrovirus, initially called ATLV, was determined [154, 193]. Comparison of

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the nucleotide sequences between HTLV-1 and ATLV revealed that these two viruses were almost identical [186].

Cloning of the HTLV-1 genome provided a molecular tool to prove the close association of HTLV-1 infection to ATL. First, the HTLV-1 provirus was detected without exception in the genome of leukemic cells from ATL patients. Second, a majority of leukemic cell from a given patient harbored the provirus at the same chromosomal site in the genome, indicating monoclonal growth of the infected cell; otherwise, the integration would occur at random in the natural retrovirus infection. Thus, it was concluded that HTLV-1 is a causative agent of ATL [154].

Nucleotide sequencing of its viral genome showed that HTLV-1 lacked a cell-derived oncogene, yet it was more complex than other oncogenic retroviruses [154]. Integration sites of the provirus in leukemic cells from different ATL patients, however, differ from each other, demonstrating the absence of insertional activation of a cellular oncogene. The two well-known mechanisms of retroviral oncogenesis, transduction and cis-activation of an oncogene, therefore did not apply to HTLV-1.

In addition to essential structural and enzymatic genes (*gag*, *pro*, *pol*, and *env*) shared by all retroviral family members [92], HTLV-1 encodes a unique pX region, which generates two regulatory (Tax, Rex) and five accessory (HBZ, p30, p12, p13, p8) proteins [25, 100]. Among them, Tax and HBZ have been shown to play pivotal roles in the viral life cycle and affect expression levels of several host genes [38, 125, 159]. Therefore, a new type of oncogenic mechanism by retrovirus, in which viral transforming proteins other than viral or cellular oncogene are involved, was presented in the development of ATL.

2.2 Genome Structure and Replication of HTLV-1

2.2.1 Structural Genes

A full-length mRNA, which is identical to genomic RNA, is translated mainly to produce a Gag precursor protein (PrGag, p55). After being assembled with genomic RNA to form viral particle, PrGag is processed by viral protease (PR) to produce the matrix (MA; p19), the capsid (CA; p24), and the nucleocapsid (NC; p15) proteins (Fig. 2.1b).

The *pro* and *pol* gene products were produced by the proteolytic cleavage of Gag-Pro and Gag-Pro-Pol fusion proteins translated from the same full-length mRNA by one and two successive slip-back of reading frame (frameshifts), respectively. Viral protease further separates the Pol protein (p98) into the reverse transcriptase (RT; p62) and integrase enzymes (IN; p49) (Fig. 2.1a).

The *env* message is a singly spliced mRNA, removing the gag and pol genes as an intron from the mRNA. The *env* mRNA is translated to a precursor Env protein and the protein is glycosylated and trimerized in the endoplasmic reticulum (ER).

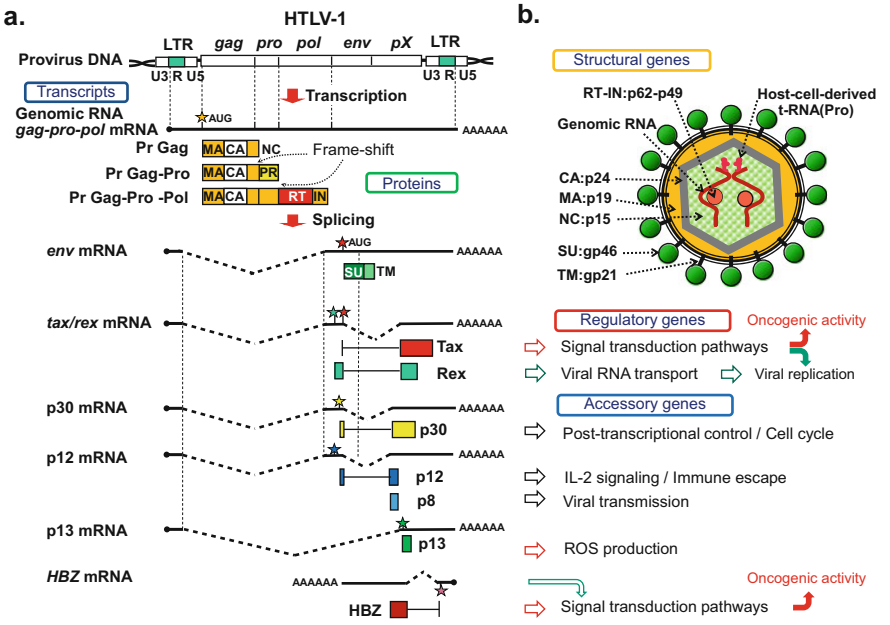

Fig. 2.1 HTLV-1 genome structure and expression of viral genes. (**a**) Schematic organization of HTLV-1 proviral DNA (*upper*), its transcripts (*lower*), and their translated products (*lower right*) are presented. (**b**) Structure of HTLV-1 virion and function of regulatory and accessory gene products

The precursor, gp68, is then cleaved by cellular protease, furin, to form the separate surface (SU; gp46) and transmembrane (TM; p21) subunits [61] (Fig. 2.1b). Cell receptor-binding activity is conferred by gp46 and the fusion activity is a function of gp21.

2.2.2 *Regulatory Proteins: Tax and Rex*

Tax and Rex are essential for efficient HTLV-1 replication and production, since HTLV-1 mutants lacking either Tax or Rex function are not able to replicate in vitro as well as in vivo [148].

Both Tax and Rex proteins are translated from an identical doubly spliced *tax*/*rex* mRNA species using different initiation codons and reading frames of translation. Tax is a transcriptional activator of HTLV-1 and thus further amplifies the HTLV-1 transcripts, mostly spliced forms, by augmenting transcriptional activity of the long terminal repeat (LTR). Once the other product, Rex, accumulates in a sufficient amount, it enhances the export of singly spliced *env* mRNA and unspliced genomic RNA encoding *gag*/*pro*-*pol*, leading to the formation of HTLV-1 particle. Nuclear export of primary unspliced and singly spliced transcripts, in turn, results in

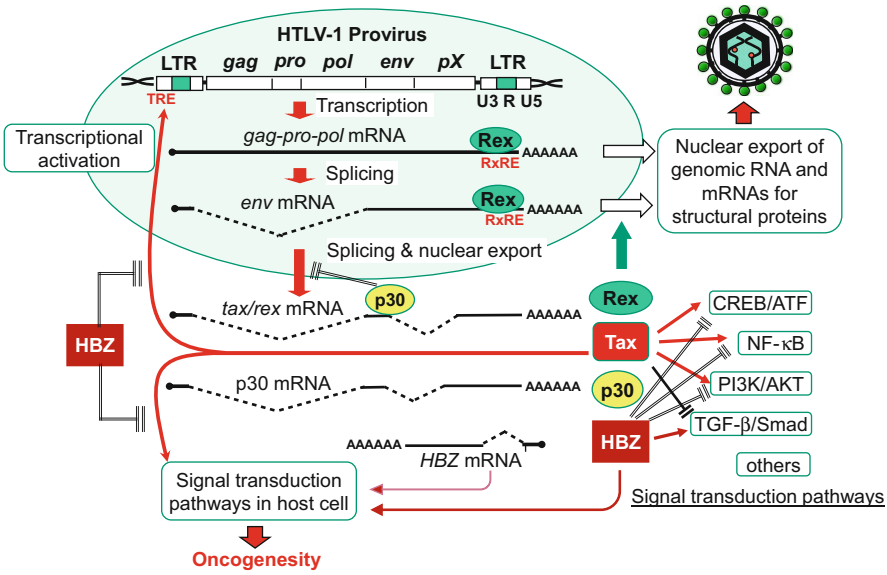

Fig. 2.2 Control of viral and cellular gene expression by viral gene products. Upon initial infection, doubly spliced mRNAs for *tax*/*rex* gene are dominantly expressed. Tax first augments viral transcription by indirect binding to TRE sequence in the HTLV-1 long terminal repeat (*LTR*) promoter, and this activity is negatively regulated by HBZ. Rex enhances the nuclear export of unspliced and singly spliced mRNAs though binding to the RxRE sequence at the 3′ end of unspliced and singly spliced mRNA, thereby increasing the translation of structural proteins, resulting in HTLV-1 virion production. p30 binds to the splice junction of *tax*/*rex* mRNA and inhibits its nuclear export. In addition, Tax and HBZ modulate a variety of cellular signaling pathways, leading to accelerated cell proliferation and induction of genome lesions. In most pathways, HBZ has opposite effects to Tax

the reduction of doubly spliced *tax*/*rex* mRNA, thereby causing the temporal cessation of transcriptional activation (Fig. 2.2).

In addition to activation of viral transcription, Tax plays pivotal roles in HTLV-1 immortalization of T cells, persistent infection, inflammation, and pathogenesis, as discussed in the following sections. Rex is essential for persistent HTLV-1 infection in rabbits but not required for immortalization of human T cells in vitro [191].

2.2.2.1 Transcriptional Activation of LTR by Tax

Tax protein of 353 amino acids long activates HTLV-1 transcription through LTR. Three highly conserved 21-bp repeat elements located within the U3 region of the LTR are critical to Tax-mediated transcriptional activation, thus referred to as Tax-responsive element (TRE) [22, 37, 42]. The TRE contains an octamer motif TGACG(T/A)(C/G)(T/A) that shares homology with the consensus cAMP-responsive element (CRE) 5′-TGACGTCA-3′ [43, 75], and a number of proteins

of the CRE-binding/activating family of transcription factors (CREB/ATF) bind to this sequence [175, 194]. Tax does not bind directly to the TRE element [44, 48] but interacts with members of CREB/ATF family, including CREB, CREM, ATF1, ATF2, ATF3, ATF4 (CREB2), and XBP1 (X-box-binding protein 1) [10, 40, 103, 112, 146, 162, 197].

Among them, CREB plays a major role in the transcriptional activation of LTR. CREB regulates several cellular genes, especially cAMP-responsive genes, and cAMP signal leads to the phosphorylation of CREB at serine 133, recruiting coactivators (CBP/p300 and P/CAF) to facilitate transcriptional initiation. The direct interaction of Tax with CBP allows the binding of the coactivator in the absence of CREB phosphorylation [104]; however, strong Tax binding to CPB/p300 requires TRE DNA and phosphorylated CREB [94]. On the other hand, Tax expression directly enhances CREB phosphorylation in vivo to ensure availability for Tax transactivation [94].

Tax also binds to CREB coactivator proteins called transducers of regulated CREB activity (TORC1, TORC2, and TORC3) [27, 72] and TORCs cooperate with Tax to activate the LTR in a CREB and p300-dependent manner [97, 158]. Downregulation of TORC2 through its phosphorylation is associated with the in vivo specific transcriptional repression of HTLV-1 LTR [78].

2.2.2.2 Posttranscriptional Regulation of Viral RNA by Rex

In addition to genomic unspliced mRNA encoding *gag*/*pol*, HTLV-1 expresses multiple mRNAs with distinctive splicings [155]. Three different singly spliced mRNAs encode *env*, *p12* and *p13*, respectively, and two doubly spliced mRNAs are for *tax*/*rex* and *p30* (Fig. 2.1).

Upon initial infection of host cells, primary transcripts with introns generally undergo splicing by the cellular RNA machinery, resulting in the preferential expression of doubly spliced *tax*/*rex* and *p30* mRNAs. Once the Rex protein accumulates, Rex binds specifically to the HTLV-1 RNA at the Rex-responsive element (RxRE) located in the U3 and R regions of the 3′ LTR [17, 179], through the interaction with a long stem-loop structure in the RxRE [18, 174]. Then Rex interacts with the nuclear export receptor protein CRM1/exportin 1, which mediates the transport of viral mRNAs from the nucleus to the cytoplasm, by the function of a typical leucine-rich nuclear export signal (NES) in Rex (aa81–94) [54]. Thus, Rex increases the amount of singly spliced (*env*) and unspliced (*gag-pol*) mRNAs and reduces the amount of its own doubly spliced mRNA by inhibiting the splicing of simply spliced (*env*, *p12*, *p13*, and *p21rex*) and unspliced (*gag*/*pro-pol*) mRNAs, stabilizing them, and promoting their transport to the cytoplasm [62, 71] (Fig. 2.2).

2.2.3 *Accessory Proteins: HBZ, p30, p12, p13, and p8*

In contrast to Tax and Rex, HTLV-1 accessory genes *HBZ*, *p30*, *p12*, *p13*, and *p8* are not absolutely required for virus replication and for the immortalization of human primary T cells in vitro [31, 105, 149]. However, investigations using animal models to study HTLV-1 infection in vivo revealed that *HBZ*, *p30*, and *p12* are essential for HTLV-1 infection and replication in nonhuman primates but *p30* and *p12* were dispensable in rabbits [181]. Human T-cell lines immortalized with HTLV-1 molecular clones lacking *p30* or *p12* grow less efficiently than their wild-type counterpart clones and more dependent on the presence of interleukin-2 (IL-2) in the media [1, 131, 170].

2.2.3.1 Viral Persistence and HTLV-1-Related Pathogenesis by HBZ

HBZ (HTLV-1 bZIP factor) is encoded by the minus strand of the HTLV-1 provirus and interacts with various host factors [3, 46, 125] (Fig. 2.1). The bZIP domain of HBZ is responsible for the interaction with the host bZIP factors, such as c-Jun, JunB, JunD [11, 172], CREB, CREB2 (ATF-4), CREM, ATF-1 [109], ATF-3 [53], and MafB [132]. The interaction mostly results in the suppression of transcriptional activity, including the Tax-mediated viral gene transcription from 5′ LTR, whereas the interaction with JunD activates transcription of target genes [172]. HBZ also enhances the TGFβ/Smad pathway, which is suppressed by Tax, through interaction with Smad2/3 and p300 [198], and then induces the expression of FoxP3 [89], a master regulatory molecule of regulatory T (Treg) cells. On the other hand, the transcriptional activity of Foxp3 is repressed by the interaction with HBZ [153]. As a result, HBZ increases the number of functionally impaired Treg cells and may lead to the development of malignancy derived from Treg cells.

Tax activates two types of NF-κB pathway, canonical and noncanonical (see the following section). p65 activation in the canonical pathway enhances the expression of CDK inhibitors p21 and p27, which cause the senescence of Tax-expressing cells. HBZ selectively inhibits the canonical NF-κB pathway by inhibiting DNA binding of p65 and promoting the degradation of p65 [199]. Thus, co-expression of HBZ with Tax delay or prevent the Tax-induced senescence, leading to cell proliferation.

Besides the functional modulation of various cellular transcription factors through protein-protein interaction, *HBZ* mRNA itself exerts a growth-promoting effect on T cells [152] (Fig. 2.1b). The first exon of the *HBZ* transcript corresponding to the R region of 3′ LTR, which forms an extensive stem-loop structure, is critical for this activity. Further details of how *HBZ* RNA promotes proliferation remain to be elucidated.

2.2.3.2 Posttranscriptional Regulation of Viral and Cellular RNA by p30

p30 is a basic 241-amino acid protein encoded by the doubly spliced mRNA distinct from *tax*/*rex* mRNA (Fig. 2.1). p30 binds to the splice junction region of *tax*/*rex* mRNA and inhibits its nuclear export, thereby reducing the expression of Tax and Rex (Fig. 2.2). Conversely, Rex interacts with p30 and counteracts its activity to induce the expression of Tax/Rex proteins [8].

p30 expression activates the G2-M cell cycle checkpoint [29] and inhibits G1-S progression and homologous recombination (HR) repair to increase the genome instability through the protein-protein interaction with cyclin E/CDK2 and Nbs1/Rad50, respectively [13, 14]. Human T cells immortalized by a HTLV-1 proviral clone defective in p30 expression were more susceptible to apoptosis induced by camptothecin, a topoisomerase I inhibitor.

2.2.3.3 Augmentation of Reactive Oxygen Production by p13

p13 is identical to the C-terminal 87 amino acids of p30 but encoded by a distinct singly spliced mono-cistronic mRNA (Fig. 2.1). A highly basic protein, p13, localizes mostly to mitochondria [28] and triggers an inward K+ and Ca+ current causing depolarization, activation of the electron transport chain, and augmentation of reactive oxygen species (ROS) production [16, 156] (Fig. 2.1b). Ectopic expression of p13 significantly reduces the incidence and growth rate of tumors arising from c-myc- and Ha-ras-co-transfected rat embryo fibroblasts [157]; therefore, low level of ROS production might help keep the infected cells benign through selectively killing the transformed HTLV-1 cells.

2.2.3.4 Modulation of Signal Transduction and Immune Response by p12/p8

p12 is a highly hydrophobic membrane protein of 99 amino acids and localized in the endoplasmic reticulum (ER) and Golgi complex [33]. p12 increases intracellular Ca^{2+} concentration by interacting with two ER resident proteins – calnexin and calreticulin – that regulate Ca^{2+} release from the ER [33]. Increased concentration of Ca^{2+} leads to the activation of calcineurin to dephosphorylate NFAT, thereby augmenting the transcription of genes such as IL-2 [2]. p12 also interacts with the beta and gamma c chain of the IL-2R and enhances the phosphorylation of STAT5 and its DNA binding [131]. Thus, p12 decreases the IL-2 requirement for T-cell proliferation and promotes cell proliferation (Fig. 2.1b).

In addition, p12 interacts with the major histocompatibility complex (MHC) class 1 heavy chain to inhibit its interaction with β2-microglobulin, thereby inducing the proteasome-dependent degradation of MHC class I [80]. The down-

modulation of MHC class I reduces CTL-mediated killing of HTLV-1 infected cells. Furthermore, p12 also reduces expression of ICAM-1 and ICAM-2 to evade NK cells, which recognize cells lacking MHC class I molecule (Fig. 2.1b).

Proteolytic cleavage of p12 removes the ER retention motifs to generate the C-terminal product p8 [182]. p8 is localized to the T-cell membrane to induce lymphocyte function-associated antigen-1 (LFA-l)-mediated cell clustering, augmenting the number and length of conduits (filopodia-like membrane extensions) which are involved in HTLV-1 transmission as discussed later (Figs. 2.1b and 2.4).

2.3 Transmission

HTLV-l is primarily transmitted from infected mother to child through breastfeeding, while sexual contact and blood transfusion are additional routes of transmission [51]. Initial infection in vivo first requires interaction with oral, gastrointestinal, or cervical mucosa except infection through blood transfer. HTLV-1 infected cells can directly bypass a disrupted mucosa [143], while HTLV-1-infected macrophages could transmigrate through an intact epithelium as observed for human immunodeficiency virus (HIV) [168, 177] (Fig. 2.3a). On the other hand, viral particles produced by HTLV-1 infected T cells have been shown to cross the epithelium within an endosome from the apical to the basal

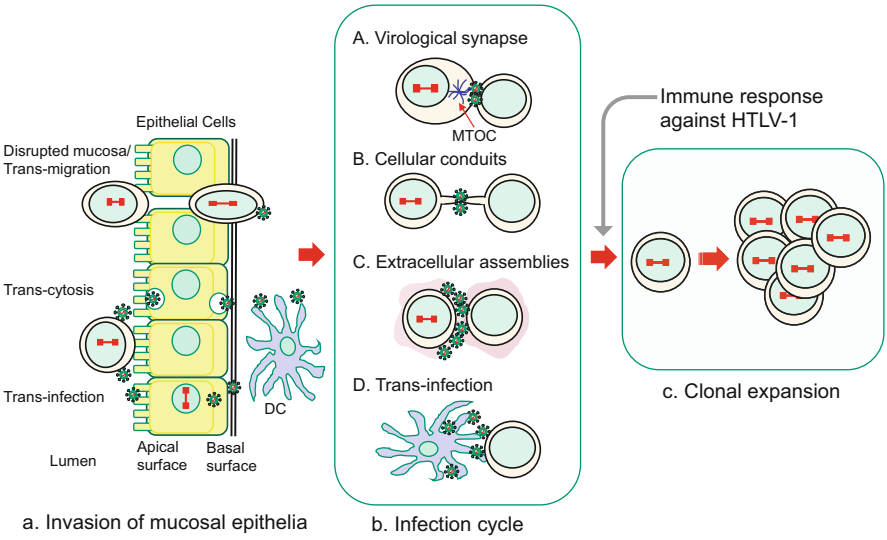

Fig. 2.3 Transmission and expansion of HTLV-1. (**a**) Three different modes of mucosal invasion of HTLV-1. (**b**) Four different modes of cell-to-cell transmission of HTLV-1. (**c**) Clonal expansion mode of HTLV-1 replication

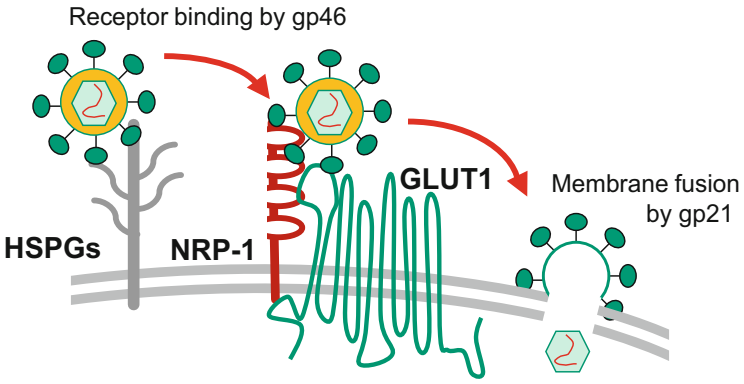

Fig. 2.4 Model of HTLV-1 entry. Gp46 subunit of envelope protein attaches to heparan sulfate proteoglycans (*HSPGs*) on the target cell, which increases the local concentration of the viruses at the cell surface. Gp46 then binds to neuropilin-1 (*NRP-1*), and this binding induces a conformational change of the subunit that facilitates its interaction with glucose transporter 1 (*GLUT-1*). The formation of a ternary complex of gp46, NRP-1, and GLUT-1 induces a conformational change of gp21 that triggers the fusion of the viral and cell membranes

surface of an epithelial cell (transcytosis) [122]. Alternatively, HTLV-1 can also infect an epithelial cell and produce new virions that are then released from the basal surface [143, 195].

Having crossed the epithelial barrier, HTLV-1 infects mucosal immune cells directly or via APCs such as DCs or macrophages. APCs can either undergo infection or transfer membrane-bound extracellular virions to uninfected T cells (trans-infection) [83]. HTLV-1 predominantly infects CD4+ T cells but also targets other cell types such as CD8+ T and B lymphocytes, dendritic cells (DCs), monocytes, and macrophages [83, 101, 116].

HTLV-1 entry into susceptible cells begins with the binding of the HTLV-1 envelope glycoprotein (Env) to a viral receptor on the membrane of the host cell, and it is followed by the fusion of viral and cell membranes (Fig. 2.4). Efficient entry of HTLV-1 has been shown to involve three distinct molecules: heparin sulfate proteoglycans (HSPGs) and neuropilin 1 (NRP-1) for the initial binding to the cell and glucose transporter 1 (GLUT1) for entry [47, 82, 107, 120]. These molecules are ubiquitously expressed and may explain the wide range of target cells, but HTLV-l might differentially utilize these molecules in a cell type-dependent manner. In the current model, HTLV-1 Env first attaches to HSPGs on the target cell, which increases the local concentration of the viruses at the cell surface. HTLV-1 Env then binds to NRP-1, inducing a conformational change of Env that facilitates its interaction with GLUT-1. The ternary complex formation of Env, NRP-1, and GLUT-1 gives rise to an additional conformational change of Env that triggers the fusion of the viral and cell membranes.

HTLV-1 transmission usually occurs through cell-to-cell contact of HTLV-1-uninfected cells with HTLV-1-infected cells, and cell-free viruses are poorly

infectious [30, 126]. Cell-to-cell transfer of HTLV-1 virions then potentially involves several nonexclusive mechanisms: a virological synapse [70, 119, 129], cellular conduits [182], or extracellular viral assemblies [81, 137] (Fig. 2.3b).

During cell-to-cell HTLV-1 transmission, the site of contact between an HTLV-1-infected cell and a target cell forms a special structure called the virological synapse (VS, named thus because of its similarity to the immunological synapse) [70] (Fig. 2.3b-A). VS formation involves polarization of the microtubule-organizing center (MTOC) near the site of cell-to-cell contact in the infected cells. ICAM-1 and Tax appear to play a role in polarization of the MTOC during cell-to-cell transmission.

HTLV-1 can also spread from an infected to an uninfected T cell by membrane extensions, which is referred to as cellular conduits [182] (Fig. 2.3b-B). HTLV-1 particles are concentrated at the point of contact between the HTLV-1-infected cell and the target cell.

Extracellular carbohydrate-rich assemblies attached to the surfaces of HTLV-l-infected cells contain infectious virions, and their removal prominently reduces cell-to-cell HTLV-1 transmission [137] (Fig. 2.3b-C). These virion-containing assemblies resemble bacterial biofilm in structure and composition and contain HSPGs, collagen, agrin, and galectin-3. When HTLV-1-infected T cells are exposed to uninfected T cells, these assemblies are quickly transferred to the target cell [137].

In addition to spreading between T cells, HTLV-1 can be transmitted from DCs to CD4+ T cells in two different ways, *cis*- and *trans*-infection. In *cis* mode of transmission, the DCs are infected, and then the de novo produced HTLV-1 is transferred to the T cells [83] (Fig. 2.3b-D). In the *trans*-infection, uninfected DCs capture and transmit the virus to T cells prior to becoming infected themselves [74].

2.4 Clonal Expansion and Immune Response

Soon after primary infection, HTLV-1 expands by reverse transcription of the viral RNA, integration of the provirus into the chromosome, expression of viral proteins, and budding of new virions (the infectious cycle, Fig. 2.3b). At this stage of infection, host restriction factors such as SAMHD1 [164], APOBEC3 [136], and miR-28-3p [7] have been shown to limit HTLV-1 infection.

An antiviral immune response is quickly initiated, and the efficacy of the infectious cycle is severely attenuated soon after infection. Then, HTLV-1 replicates through another mode of replication which involves mitotic division of a cell containing an integrated provirus (the clonal expansion, Fig. 2.3c). The limited variability in the HTLV-1 genome compared to HIV suggests a replication mode by cellular DNA polymerase rather than by error-prone viral reverse transcriptase in a major part of viral expansion. In fact, high-throughput sequencing of proviral integration sites reveal a high clonal stability over years [50].

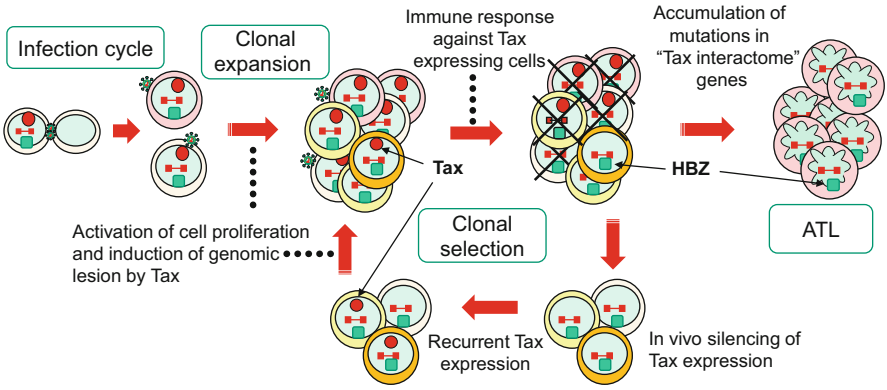

Fig. 2.5 Model of clonal selection and ATL development. In early stage of infection, Tax and HBZ promote the proliferation of infected cells as well as the induction of genomic lesions (clonal expansion). Because of strong immunogenicity of Tax, Tax-expressing cells are rapidly eliminated. However, a substantial part of infected cells is escaped from the immune response due to the in vivo specific silencing mechanism of viral expression. Repetitive cycles of viral expression followed by transcriptional silencing lead to clonal selection and accumulation of mutations, finally in genes of Tax interactome, a network of molecules that Tax physically interacts with and/or deregulates, in ATL

On the other hand, clonal expansion and cell proliferation also require expression of viral factors such as Tax [19]. The in vivo proliferation of CD4+ T cells correlates with Tax expression [6]. Because Tax is a major target of CTLs [73, 84], Tax-expressing cells are rapidly eliminated (Fig. 2.5). However, transcription of the *tax* gene from the 5′ LTR is suppressed in vivo, and ex vivo culture of HTLV-1-infected cells elicits a rapid recovery of the tax gene expression [173], indicating a mechanism of inhibiting viral gene transcription in vivo [45, 56, 78]. Thus, repetitive cycles of viral expression followed by transcriptional silencing continuously challenge the immune response, thereby initiating inflammation and ultimately leading to HAM/TSP. Identification of integration sites by high-throughput sequencing shows that negative selection is predominant in chronic infection [50]. By favoring emergence of sporadic mutations in the cell genome, unrestrained proliferation also paves the way to malignant transformation and development of ATL [6, 91] (Fig. 2.5).

2.5 Leukemogenesis by Tax and HBZ

Among an array of viral factors, Tax and HBZ play a major role in leukemogenesis of HTLV-1 infected cells. Tax immortalizes human T cells in the presence of IL-2 and transforms rat fibroblasts and drives tumor formation in transgenic mouse models, supporting its oncogenic potential [52, 60, 133]. Mutation of the *tax* gene

in recombinant HTLV-1 abrogates immortalization as well as persistent infection in rabbits [148].

Although HBZ is dispensable for the HTLV-1-mediated T-cell transformation in vitro, it plays an indispensable role in persistent viral infection in vivo [3]. In transgenic mouse model, HBZ expression in CD4 T cells induces chronic inflammation and T-cell lymphoma [153]. Furthermore, HBZ is constitutively expressed throughout HTLV-1 infection [91, 124, 180], whereas Tax expression is frequently suppressed or diminished in ATL cells [91, 98, 167], indicating the role of HBZ in maintaining the transformed phenotype [125]. Because of the strong immunogenicity of the Tax protein, these mechanisms can confer a selective advantage to HTLV-1-transformed T cells [73, 84, 86] (Fig. 2.5). In contrast, HBZ triggers a less efficient immunity that renders its persistent expression in vivo [64, 117].

An integrated genome analysis of a large number of ATL cases revealed that the driver mutations overlap significantly with the Tax interactome [19], a network of molecules that Tax physically interacts with and/or deregulates [91]. Thus, it seems that ATL cells still depend on deregulated Tax interactome molecules, even though Tax itself is no longer expressed in most ATL cases.

The modes of action of Tax and HBZ are remarkably pleiotropic and involve a variety of cell signaling pathways (CREB, NF-κB, and AKT, Fig. 2.2).

Tax inhibits tumor suppressors (p53 [147], Bcl11B [166], and TP53INP1 [192]) and activates cyclin-dependent kinases (CDKs) [55, 69, 134, 151], both of these mechanisms leading to accelerated cell proliferation. In addition, Tax induces genomic instability [20, 21, 23, 95], generating somatic alterations [121], and attenuates the Mad1 spindle assembly checkpoint protein, thereby promoting aneuploidy [79].

HBZ counteracts Tax-mediated viral and cellular pathway modulation (such as NF-κB, Akt, and CREB) and stimulates cell proliferation via apoptosis/senescence inhibition and cell cycle modulation [4, 152]. The interaction of HBZ with AP-1 factors (c-Jun, JunB, or MafB) results in the inhibition of their transcriptional activities and prevents the subsequent activation of AP-1-regulated genes [26, 67, 123].

2.5.1 Activation of NF-κB

The NF-κB pathway is a key player in regulation of immunity and inflammation [161], and Tax activates the transcription factor NF-κB, thereby inducing the expression of several cellular genes. HTLV-1 carrying a mutant Tax that cannot activate NF-κB fails to immortalize human T cells in vitro [148]. Moreover, several NF-κB inhibitors induce apoptosis in HTLV-l-infected T cells. Thus, the NF-κB activity is crucial for the immortalization and the survival of HTLV-1 infected T cells.

By activating the NF-κB pathway, Tax upregulates antiapoptotic proteins: caspase-8 inhibitory protein c-FLIP [102, 135] and members of the Bcl-2 family

(Bcl-2, Bcl-xL, Mcl-1 and Blf-1) [115, 130, 163, 176], thereby supporting the proliferation and survival of HTLV-1-infected T cells. A variety of growth-promoting cytokines (such as IL-1, IL-6, TNF, and EGF) [88, 187] are also induced by Tax through the activation of NF-κB.

Conversely, NF-κB activation by Tax is associated with an upregulation of $p21^{WAF1/CIP1}$ and $p27^{KIP1}$, leading to cellular senescence [68, 200]. Instead, HBZ prevents Tax-induced senescence through downregulation of NF-κB [141, 200].

NF-κB is a family of transcription factors, and these factors are divided into two groups belonging to the canonical (NF-κB1/p50, p65, c-Rel) and the noncanonical (NF-κB2/p52, RelB, Bcl-3) pathways. Tax activates both pathways.

Through interacting with IKKγ/NEMO, a scaffold component of the IκB kinase (IKK) complex (IKKα/IKKβ/IKKγ), Tax activates the IKKβ to induce phosphorylation and degradation of IκBs (IκBα, IκBγ), allowing nuclear translocation of p50/p65 complex to activate transcription of NF-κB-responsive genes (canonical pathway) [58, 161]. Concurrently, the IKKα is activated to phosphorylate p65, which stimulates its transcriptional activation function.

Tax interaction with another IKK complex composed of IKKα and IKKγ, but not IKKβ, induces IKKα-dependent processing of p100 into p52 [58, 161] and the subsequent nuclear translocation of p52/RelB (noncanonical pathway). Knockdown of NF-κB2/p100 abrogates the Tax-induced transformation of CTLL-2 cell in vitro [63], and the knockout of NF-κB2/p100 gene attenuates the tumorigenesis in Tax transgenic mouse [41].

Although the constitutive activation of NF-κB pathway is crucial for the transformed phenotype of HTLV-1-infected T cells, ATL cells often lack the Tax expression due to deletions or epigenetic silencing of the 5′ LTR or mutations in Tax [66, 167]. The mechanisms of Tax-independent chronic activation of NF-κB remain poorly understood but may result from epigenetic alterations. Epigenetic downregulation of microRNA-31 (miR-31) in ATL promotes increased the expression of NIK (NF-κB-inducing kinase) that activates IKKα and noncanonical NF-κB pathway [189]. The expression of NIK is also enhanced by double-stranded RNA (dsRNA)-dependent protein kinase (PKR) that is activated by antisense transcripts at R region detected in all ATL cases [96].

2.5.2 Activation of the PI3K/AKT Pathway

Tax promotes cell proliferation and survival through the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [140]. Tax directly interacts with the p85α inhibitory subunit of PI3K, causing the release of the active p110α catalytic subunit [140]. Inhibition of Akt in HTLV-1-transformed cells decreases phosphorylated Bad and induces caspase-dependent apoptosis [77].

In contrast, HBZ inhibits Tax-dependent activation of the PI3K/Akt pathway and downstream antiapoptotic properties [160]. HBZ suppresses apoptosis by attenuating the function of FOXO3a and altering its localization [169].

2.5.3 Modulation of TGF-β/Smad and Wnt Signaling Pathways

Tax represses TGF-β signaling by blocking the association of Smad proteins with Smad-binding elements [108] and via c-Jun activation [5]. Conversely, HBZ interacts with Smad2/3 to enhance TGF-β/Smad transcriptional responses in a p300-dependent manner, improving transcription of different genes, such as the FOXP3 mediator of regulatory T cells [198]. This activation also results in the enhanced transcription of Wnt5a, a key protein of the noncanonical Wnt pathway. Knockdown of Wnt5a represses proliferation and migration of ATL cells, indicating the role of this pathway in HTLV-1-infected cell growth [113].

Tax interacts with DAPLE (dishevelled-associating protein with a high frequency of leucine residues) to activate the canonical Wnt pathway, whereas HBZ suppresses this activation by inhibiting DNA binding of TCF-1/LEF-1 transcription factors in the downstream.

2.5.4 Enhancement of S Phase Entry and Cell Cycle Progression

Through interaction with cyclins and CDKs, Tax interferes with cell cycle progression by several mechanisms. By stabilizing the cyclin D2/CDK4 complex and repressing cyclin-dependent kinase inhibitors (CKIs) such as members of INK4 family and KIP1, Tax enhances the phosphorylation of retinoblastoma protein (Rb) to free E2F1 that activates transcription of genes required for G1/S transition.

Tax also activates the cyclin D1 transcription via CREB pathway, thereby enhancing S phase entry of HTLV-1 infected cells, whereas HBZ interacts with CREB and inhibits transcription of cyclin D1 [114]. Early firing of late replication origins by Tax is associated with p300-dependent histone hyperacetylation, and interaction of Tax with the replicative helicase (minichromosome maintenance complex, MCM2-7) also accelerates S phase progression [20].

In contrast to Tax, HBZ modulates expression of cell division cycle 2 (CDC2) and cyclin E2 through interaction with activating transcription factor 3 (ATF3), thereby promoting proliferation of ATL cells [53]. Concomitantly, HBZ suppresses ATF3-induced p53 transcriptional activity. Moreover, the growth-promoting effect of *HBZ* mRNA on T cells is correlated with the enhanced transcription of E2F1 gene [152].

2.5.5 *Induction of Chromosomal Abnormality and DNA Damage*

The tumor-suppressor protein p53, the main factor that controls G1 checkpoint, is functionally inactivated in leukemic and HTLV-1 transformed cells [165]. NF-κB p65 subunit is critical for Tax-induced p53 inactivation [144] and wild-type p53-induced phosphatase 1 (Wip1) is involved in the inactivation [49, 196].

ATL cells are characterized by loss of spindle assembly checkpoint function [90] and aneuploidy [190]. Tax binding to Mad1 perturbs the organization of the spindle assembly and results in multinucleated cells [79]. Tax also interacts with the anaphase-promoting complex APC Cdc20, inducing the mitotic abnormalities in HTLV-1-infected cells [111].

Firing of supplementary origins of replication by Tax triggers replicative stress and genomic lesions, such as double-strand breaks (DSBs) [21, 23], which generate reactive oxygen species (ROS) [95]. Tax-associated DNA damages activate several phosphoproteins of the DDR pathway (H2AX, ATM, CHK1-2, P53, BRCA1), which in turn arrest the cell cycle transiently or lead to apoptosis and senescence. In the presence of DNA-damaging agents (e.g., UV irradiation), Tax inhibits the DDR machinery by sequestrating key signaling pathway components [15, 24, 35, 57, 138, 139]. Induction of genomic lesions and inhibition of the DDR leads to proliferation in presence of DNA mutations, potentially to leukemogenesis.

HBZ also induces DNA lesions through activation of miR-17 and miR-21 and downregulation of the DNA damage factor OBFC2A [183] and deregulates the cellular responses to DNA damage by inhibiting the activity of growth arrest and DNA damage gene 34 (GADD34) [128].

In addition, Tax has negative effects on DNA repair pathways. Downregulation of β-polymerase transcription by Tax [76] leads to the inhibition of base excision repair (BER) [142]. Tax interferes with nucleotide excision repair (NER) by activating PCNA [87, 110] and suppresses nonhomologous end joining (NHEJ) by repressing Ku80 gene transcription and also by interacting with Ku80 protein [34, 118], while DSBs are preferentially repaired by error-prone NHEJ in Tax-expressing cells [12].

2.6 Animal Model

To evaluate viral pathogenesis and elucidate the function of viral products in vivo, a variety of animal models have been established [9, 32, 39, 45, 60, 99, 153, 184]. The Tax transgenic mouse, which expresses Tax under the control of the Lck promoter, results in characteristic ATL-like phenotypes [60]. The HBZ transgenic mouse, which expresses HBZ under the control of a CD4-specific promoter/enhancer/silencer, develops lymphomas characterized by induction of Foxp3 in CD4 T cells, similar to leukemic cells in ATL patients [153].

In addition to transgenic mouse models, a number of HTLV-1-infected small-animal models have provided valuable findings regarding virus-host interactions; however, they are unable to fully recapitulate pathological conditions resembling ATL, likely due to the low efficiency of HTLV-1 infection [93, 106].

As immune responses against HTLV-1 play a pivotal role in controlling the proliferation or selection of HTLV-1-infected T-cell clones in vivo [59, 85], animal models of ATL that induce more humanlike HTLV-1-specific immune responses are required for analysis of the development of ATL. Humanized mice are highly susceptible to infection with human lymphotropic viruses, such as EBV, HIV-1, and HTLV-1, and are able to recapitulate specific disorders and human immune responses [184, 185, 188]. HTLV-1 infection of humanized mouse, which is produced by the intra-bone marrow transplantation of human hematopoietic stem cells, displayed distinct ATL-like symptoms, including hepatosplenomegaly, hypercytokinemia, oligoclonal proliferation of HTLV-1-infected T cells, and the appearance of flower cells [171]. Furthermore, HTLV-1-specific immunity was induced.

2.7 Perspective

Since the discovery of HTLV-1, extensive studies have revealed a complex network of interactions between viral genes and host factors. This network controls the expression of viral genes and facilitates persistent infection by allowing evasion of the host immune response and promoting the proliferation of infected cells.

Recent findings from the integrated molecular study of ATL genome provide a strong evidence for the notion that the aberrant growth-promoting activities attributed to Tax function are taken over by mutations in genes belonging to the Tax interactome [91]. Knowledge of the genes and the mutations will guide the development of new diagnostics and therapeutics for ATL.

As the incident rate of mutations correlates with the number of infected cells and, probably, with Tax expression during persistent infection, it is important to control the viral expression and the clonal expansion of infected cells in vivo to suppress the onset of ATL. Therefore, further analysis with suitable animal model of HTLV-1 infection, in which anti-HTLV-1 immune response is established, should provide vital information for developing antiviral and/or preventive therapy.

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