Review

Human T-cell lymphotropic virus type 1 and its oncogenesis

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Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia/lymphoma (ATL), a rapidly progressing clonal malignancy of CD4⁺ T lymphocytes. Exploring the host-HTLV-1 interactions and the molecular mechanisms underlying HTLV-1-mediated tumorigenesis is critical for developing efficient therapies against the viral infection and associated leukemia/lymphoma. It has been demonstrated to date that several HTLV-1 proteins play key roles in the cellular transformation and immortalization of infected T lymphocytes. Of note, the HTLV-1 oncoprotein Tax inhibits the innate IFN response through interaction with MAVS, STING and RIP1, causing the suppression of TBK1-mediated phosphorylation of IRF3/IRF7. The HTLV-1 protein HBZ disrupts genomic integrity and inhibits apoptosis and autophagy of the target cells. Furthermore, it is revealed that HBZ enhances the proliferation of ATL cells and facilitates evasion of the infected cells from immunosurveillance. These studies provide insights into the molecular mechanisms by which HTLV-1 mediates the formation of cancer as well as useful strategies for the development of new therapeutic interventions against ATL. In this article, we review the recent advances in the understanding of the pathogenesis, the underlying mechanisms, clinical diagnosis and treatment of the disease caused by HTLV-1 infection. In addition, we discuss the future direction for targeting HTLV-1-associated cancers and strategies against HTLV-1.

Keywords: human T-cell lymphotropic virus type 1; adult T-cell leukemia/lymphoma; Tax; HBZ; tumorigenesis; innate immunity

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Introduction

Human T-cell leukemia viruses (HTLVs), belonging to the primate T-lymphotropic virus (PTLV) family^[1], are complex retroviruses. HTLVs are classified as the Delta-retroviruses genera of the Orthoretrovirinae subfamily^[2]. Approximately 30 000–40 000 years ago, simian T-lymphotropic viruses (STLVs) were transmitted from monkeys to humans in Africa and gradually evolved into HTLVs. Since then, HTLVs have spread to different geographic regions with human migration^[3]. Nevertheless, STLVs, having high homology to HTLVs, still exist in Africa^[4]. To date, four types of HTLVs, *ie*, HTLV1/2/3/4, have been identified. HTLV-1, the first oncogenic HTLV in humans, was originally discovered in the early 1980s by two independent research groups in America and Japan^[2, 5]. The virus predominantly infects T lymphocytes, and its genome is composed of a positive single-stranded RNA^[6]. HTLV-1, including its seven

subtypes (HTLV-1A to -1G), is endemic in Japan, Melanesia, Iran, Central and West Africa, the Caribbean, Australia, and the Middle East^[7, 8]. It is estimated that approximately 10 million people are infected with HTLV-1 around the world, but most of them remain asymptomatic throughout the rest of their lives^[7]. Only a small proportion (2%–5%) of HTLV-1-infected humans progress to adult T-cell leukemia/lymphoma (ATL), a very aggressive form of leukemia^[9]. Another important HTLV-1-associated disease is HAM/TSP (HTLV-associated myelopathy/tropical spastic paraparesis), a type of neurological demyelinating disease^[10, 11]. In addition, three other genotypes of HTLVs, namely, HTLV-2, HTLV-3, and HTLV-4, have been isolated and characterized^[12]. HTLV-1 and HTLV-2 are more prevalent than HTLV-3 and HTLV-4^[12]. Although the CD4⁺ T-cell are the main target cells of HTLV-1, many other types of cells, such as CD8⁺ T-cell, endothelial cells, B-lymphocytes, myeloid cells, and fibroblasts, can also be infected with HTLV-1^[13, 14]. Therefore, HTLV-1 is a significant threat to public health. In this article, we highlight the

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current knowledge of HTLV-1, including HTLV-1-mediated oncogenesis, the critical proteins encoded by HTLV-1 and the mechanisms underlying their functions during viral infection. In addition, we also review the strategies for the prevention of HTLV-1-associated cancer and the future direction of cancer research in the field of HTLV-1.

Genotypes of HTLVs

Four genotypes of HTLVs have been found as described above. HTLV-1 can be transmitted via body fluids, e.g., blood, breast milk and semen^[15]. Transmission from mother to child occurs primarily via breast-feeding and rarely through transplacental or intrapartum transmission in endemic regions^[16, 17]. In most cases, sexual transmission occurs from a man to a woman during sexual intercourse^[15-17]. Moreover, human-to-human parallel transmission, primate-to-human transmission, and non-human transmission have also been observed^[18].

Previous studies have sought to determine the mechanism underlying the oncogenesis of HTLV-1. It has been shown that HTLV-1, unlike other acute transforming retroviruses, is neither able to induce tumors rapidly nor able to upregulate the expression of cellular proto-oncogenes^[19]. In general, viral infections can initiate and promote tumorigenesis by any of the following mechanisms: induction of chronic inflammation in the host, suppression of the host immune defense, insertional mutation in the host genome and activation of virally carried oncogenes that mediate cellular transformation^[20-22]. Studies have demonstrated that HTLV-1-induced oncogenesis may involve multiple mechanisms^[19, 23, 24]. First, a prolonged and persistent infection with HTLV-1 results in chronic inflammation in the host. Then, phagocytes release reactive oxygen species at the inflammatory site, which interact with nitrogen radicals, causing damage to the cell membrane, DNA and proteins and altering the gene expression profiles and enzymatic activities. Consequently, these responses induce carcinogenesis and enhance neoplasia^[23]. Second, HTLV-1 infection can cause the insertion of efficient oncogenes into the host genome, which reduce the expression of tumor suppressor genes or directly stimulate mitosis of the host cells^[24]. Third, HTLV-1 infection can also inhibit the host immune function and impair immune surveillance, and thus, pre-cancerous cells can escape from host immunity^[24]. However, novel insights into the precise mechanisms by which HTLV-1 induces tumorigenesis are expected to be discovered in the future using new approaches.

Importantly, it is thought that HTLV-1 infection happens early in life and has a long latency period before cancer appears. Thus, the vast majority of effort has focused on the prevention of HTLV-1-mediated tumorigenesis. Because the exposure to HTLV-1 in early life plays an important role in cancer development later in life, it is practical to develop interventions targeting early life exposure to the infection^[25].

HTLV-2 was initially described in 1982^[26]. Molecular biology experiments have defined four major subtypes of HTLV-2, namely, HTLV-2A/B/C/D^[27]. HTLV-2 is endemic within the Amerindian and Pygmy populations and epidemic among intravenous drug users, with 3–5 million cases worldwide^[28].

HTLV-2 is relatively less pathogenic than HTLV-1. Occasionally, HTLV-2 infection ends in sub-acute neurological syndromes, such as neuropathies and paraparesis, despite being very rare^[29, 30].

Human HTLV-3 and HTLV-4 are two new members of the HTLV family. In 2005, Gessain's group and others reported the discovery of the human HTLV-3 in two asymptomatic inhabitants of South Cameroon. A fourth HTLV type (HTLV-4) was also discovered in the same geographical area^[31, 32]. Interestingly, recent molecular biology investigations have shown that HTLV-4 lineage is older than the ancestors of HTLV-1, HTLV-2 and HTLV-3^[33]. Although a number of distinguishing characteristics of HTLV-3 and HTLV-4 have been revealed, the pathogenic potential of these human retroviruses remains to be determined.

Notably, the original name for human immunodeficiency virus (HIV), the virus isolated by Gallo's team in 1984, was HTLV-III^[34], but it has since fallen out of use. Collectively, it was demonstrated that HIV was the cause of a new epidemic, AIDS^[35]. Like HTLV-1, similar risk factors were observed for HIV-1 infection, including blood exposure, sexual contact, and birth to a mother with the disease^[36]. Both HTLV-1 and HIV-1 target cells of the immune system, particularly CD4+ T-cell, and cause them to grow abnormally (HTLV-1) or die (HIV-1). In addition, they encode regulatory proteins essential for viral replication, such as TAX, Rex (HTLV-1), and Tat, Rev (HIV-1)^[35, 37]. However, although HTLV-1 and HIV-1 share similar routes of transmission, they cause significantly different diseases. ATL is the major disease caused by HTLV-1 infection, while infection with HIV-1 ultimately results in deficiency of the human immune system.

Biological structure of HTLVs and their components

Similar to other retroviruses, HTLV-1 begins its life cycle by targeting specific cells. HTLV-1 contains an RNA genome in the virion^[38]. Upon viral entry, the viral RNA is reverse transcribed into a double-stranded DNA, which can be integrated into the DNA genome of the host cell, resulting in the provirus^[39]. HTLV-1 has a relatively small (9 kb) genome, but it can express multiple products by utilizing various strategies, including polycistronic translation, frame shifting, alternative mRNA splicing, and protease-mediated cleavage of large viral proteins into smaller polypeptides with specific functions^[40].

All four HTLVs have similar genomic structures, as demonstrated by comparative studies of their genomic sequences^[1]. HTLV-1 and HTLV-2 have common molecular features and exhibit approximately 70% nucleotide sequence homology^[28]. HTLV-3 has approximately 62% nucleotide sequence homology with HTLV-1, and HTLV-4 shares approximately 62%–71% sequence identity with HTLV-1, HTLV-2, and HTLV-3^[41]. However, there is one major difference between the nucleotide sequences of HTLV-1/2 and HTLV-3/4: the long terminal repeats (LTRs) of HTLV-3/4 lack the distal 21-bp transcription regulatory repeat sequences, *ie*, Tax-responsive elements (TREs), and possess only two 21-bp repeat sequences, while the LTRs of HTLV-1/2 have three of these 21-bp repeat

sequences^[41, 42]. In addition to the two LTR-containing cis-acting regulatory sequences of the provirus, all four HTLV genotypes contain the structural genes *gag*, *pro*, *pol*, and *env* and the regulatory genes *tax* and *rex*^[38] (Figure 1).

One region (named PX) located downstream of the envelope gene of HTLVs contains several open reading frames (ORFs) encoding auxiliary proteins. HTLV-1 encodes four different auxiliary proteins, including p13, p30, p12 and p8^[43] (Figure 1). These proteins play crucial roles during HTLV-1 infection. p30 decreases the expression of Tax, a viral transcription transactivator, thus promoting viral latency and persistence and helping the virus escape from immune surveillance^[44]. Similar to p30, p13 also enables the virus to bypass immune surveillance by increasing the production of mitochondrial ROS (reactive oxygen species)^[45]. As a result, p13 may promote viral latency and persistence^[46]. p12 inhibits the activation of cytotoxic T lymphocytes (CTLs) and natural killer cells (NK), hence protecting the virus against immune surveillance. p8, a proteolytic cleavage product of p12, accelerates T-cell contact by augmenting the number and length of cellular conduits among T-cell and enhances the envelope-dependent transmission of HTLV-1^[47]. In addition to the proteins p13 and p30, HTLV-2 also encodes regulatory and accessory proteins, such as p10, p11 and p28. Given the genomic features

of HTLVs, more potential ORFs encoding auxiliary proteins may be discovered in the future^[1]. For example, HTLV-2 contains a potential ORF called APH-2 on its antisense strand, which is analogous to HTLV-1 bZIP factor (HBZ), an antisense transcript of the HTLV-1 provirus^[48, 49], as well as APH-3/4 of HTLV-3/4^[50]. Sequence analysis has demonstrated that APH-3 and APH-4 are more closely related to APH-2 than to HBZ^[50]. APH-2, APH-3 and APH-4 do not contain a bZIP (basic leucine zipper) domain, which is present in HBZ. Additionally, APH-2, APH-3 and APH-4 differ from HBZ in their subcellular localization^[48, 50]. The Tax gene, located between *env* and 3'-LTR, is encoded within the pX region of HTLVs and is highly conserved among four genotypes and different subtypes of HTLVs^[51]. The structural and functional domains of Tax-1, Tax-2, Tax-3, and Tax-4 are shown in Figure 1.

Invasion of HTLV-1 and HTLV-1-mediated cellular transformation

The invasion of HTLV-1 marks the beginning of the viral survival and replication^[52]. HTLV-1 binds to its receptor on the target cells, which initiates the invasion process^[52]. The receptor complex is composed of glucose transporter (GLUT1), heparin sulfate proteoglycan (HSPG) and the VEGF-165 receptor neuropilin-1 (NRP-1)^[53, 54]. HTLV-1 interacts with HSPG,

Figure 1. Schematic representation of HTLV-1 and HTLV-2/3/4 genomes. p19 and p24 are the major core proteins of HTLVs. Gray: LTR, Long Terminal Repeat; Coding regions for all major proteins: *gag*, group-specific antigen; *pro*, protease; *pol*, polymerase; *env*, envelope; *rex*, regulator of expression; *tax*, transactivator; HBZ, HTLV basic leucine zipper. The pink letters indicate the positions of the major proteins encoded by the corresponding genes, including the MA (matrix), CA (capsid), NC (nucleocapsid) proteins of *gag*, the PR (protease), RT (reverse transcriptase), IN (integrase) enzymes of *pol* and the SU (surface) and TM (transmembrane) proteins of *env*.

followed by NRP-1, to form a complex. Then, a fusion process occurs via the combination of GLUT1 with the HSPG/NRP-1 complex^[52-54]. Afterwards, a viral core containing the viral RNA is delivered into the cytoplasm of the target cells. After reverse transcription, HTLV-1 integrates its genome into the host genome to form a provirus, flanked by two LTRs at the 5' and 3' regions. Next, the provirus transcribes and encodes structural regulatory and accessory proteins. Subsequently, the viral genomic RNA and Gag, Env and Gag-Pol proteins are transported to the plasma membrane to assemble into an immature viral particle^[55]. The budding particle is then released from the cell surface and undergoes a maturation process to form a mature and infectious viral particle^[56]. Viral Rex plays an important role in the productive phase of the viral infection and is needed for efficient viral replication. Therefore, Rex is critical for the virus to establish a successful infection^[40].

Telomerase activity is required for avoiding replicative senescence and supports immortalization of cells^[57]. While telomerase activity is absent in normal somatic cells, induction of telomerase expression is a hallmark of cancer cells^[58]. Telomerase is a holoenzyme consisting of several subunits, such as hTR (human telomerase RNA) and hTERT (human telomerase reverse transcriptase)^[59]. hTERT acts as a cellular reverse transcriptase and can extend telomeric ends, and therefore, it is the rate-limiting factor for telomerase activity^[60]. Previous studies have demonstrated that HTLV-1 is able to directly elevate hTERT expression and hTERT activity^[61]. However, initial findings on the regulation of hTERT by Tax are controversial^[61, 62]. Further experiments have demonstrated that the regulation of the hTERT promoter by Tax is dependent on the cell cycle. Tax positively regulates the hTERT promoter in resting T-cell but negatively regulates it in activated T-cell^[63]. Tax is able to recruit E2F to a 43-bp region of the hTERT promoter to positively mediate telomerase expression. Tax is also known to stimulate the transcription of two positive telomerase regulators c-myc and Sp1 through the activation of NF- κ B^[57, 64, 65]. In addition to Tax, another viral protein, HBZ, has been found to stimulate the transcription of hTERT in a JunD- and SP-1-dependent manner^[66]. Furthermore, HBZ can degrade the T-cell acute lymphoblastic leukemia 1 protein (Tal1), thus preventing the Tal1-dependent degradation of hTERT mRNA^[57]. Taken together, these observations indicate that the reactivation of hTERT expression by HTLV-1 contributes to cellular transformation during HTLV-1 infection.

Roles of HTLV-1 genes in tumorigenesis

HTLV-1 is etiologically linked to adult T-cell leukemia/lymphoma (ATL)^[8]. The genetic structure and regulation of HTLV-1 are more complex than those of other leukemia viruses^[2]. In addition to the structural genes (*gag*, *pro*, *pol*, and *env*) encoding the characteristic virion proteins, the genome of HTLV-1 also carries genes that encode the nonstructural proteins, Tax and HBZ, which are needed for regulating viral gene expression^[38]. Although considerable progress has been made in understanding the intricate mechanism of ATL caused by

HTLV-1, further investigation is required to elucidate the function and regulation of the viral gene products and their interactions with one another, as well as with cellular factors.

Tax of HTLV-1 plays an essential role in cellular transformation and interaction with the host innate immune system

Early studies have shown that Tax-1 is predominantly localized in the nucleus and accumulates specifically in the speckled structures of the nucleus^[67, 68]. Recently, it has been reported that Tax-1 is also localized in the cytoplasm^[69-71], although the mechanism regulating the subcellular localization of Tax-1 remains to be elucidated. The N-terminal region of Tax-1 contains a CREB-binding region^[72], which is required for its interaction with proteins involved in cell cycle progression, transcription and cell signaling regulation^[73, 74]. Additionally, Tax-1 interacts with cellular factors such as CAMP response element binding protein (CREB) and transcriptional co-activator CBP/p300^[75]. As a viral oncoprotein, Tax-1 plays a critical role in tumorigenesis and contributes to the pathogenesis of ATL by regulating several intracellular signaling pathways, including I κ B kinase (IKK)/NF- κ B signaling pathway^[76], DNA damage repair pathway, and the innate immune signaling pathways, such as RIG-I/MDA5-dependent and TLR-independent pathways, TRIF-dependent TLR pathways and the recently discovered cGAS-STING pathway^[77, 78].

Tumor cells are typically characterized by genetic and phenotypic instability, referred to as the mutant phenotype^[79]. Due to internal (metabolic) and external (genotoxic stress) factors as well as errors in DNA replication, genomic injuries can occur^[80]. Typically, these errors are corrected immediately by numerous cellular repair mechanisms^[79]. If these repair pathways cannot be tightly coordinated, the genomic lesions may develop into mutations during cell division and DNA replication, thereby leading to genomic instability. It is thought that a prominent feature of HTLV-1 transformed cells is the genomic instability that is caused by Tax-1-mediated inhibition of the cellular DNA repair pathways^[81] and increased mutations in the cellular genome^[80]. The random nature of these mutations indicates that this viral protein could directly and indirectly interfere with the DNA damage repair pathways, including BER (base excision repair), NER (nucleotide excision repair), MMR (mismatch repair), NHEJ (non-homologous end joining) and HR (homologous recombination). In particular, Tax-1 has been demonstrated to suppress the NER pathway through the transactivation of PCNA (proliferating cell nuclear antigen), a cofactor for DNA polymerase δ that plays a crucial role in DNA replication and repair^[82, 83]. In addition, by the inactivation of p53, Tax-1 can interfere with the function of the tumor suppressor^[84]. Tax-1 has a dose-dependent dual effect on NER. High levels of Tax-1 increase the levels of p53 but inactivate p53 function, leading to the inhibition of p53-dependent NER. However, low levels of Tax-1 stimulate NER by increasing the transcriptional activity of p53^[85].

Additionally, Tax-1 can disturb cell cycle progression, leading to aberrant proliferation of the HTLV-1-infected T-cell^[79]. Persistent activation of NF- κ B is crucial in supporting T-cell

survival and malignancy. Tax-1 directly targets the beclin1-containing autophagy molecular complex to deregulate autophagy by stimulating the IKK complex, resulting in the persistent activation of NF- κ B^[76, 86]. Autophagy not only has significant roles in preventing inflammation and viral infections but also suppresses tumorigenesis by maintaining chromosomal integrity^[87]. A previous report has shown that Tax-1 induces the production and secretion of pro-inflammatory cytokines, leading to activation of the IL-6/STAT3 pathway in HTLV-1-transformed T-cell^[88]. It is thought that when chronic inflammation is present, the risk of tumor occurrence increases.

Viral HBZ promotes cell proliferation and modulates multiple host factors contributing to tumorigenesis

In 2002, a new open reading frame (ORF) was identified in the minus strand of HTLV-1, which encodes a novel basic leucine zipper factor called HBZ^[89]. HBZ plays indispensable roles in regulating genomic integrity, cell proliferation, apoptosis, autophagy and immune escape^[49]. HBZ modulates cell growth by forming heterodimers with host factors, such as CCAAT/enhancer binding protein- α (C/EBP α) and activating transcription factor 3 (ATF3)^[90]. C/EBP α usually acts as a negative regulator of cancer cell proliferation^[90]. HBZ can overcome the suppressive effect of C/EBP α on cell growth by interacting with C/EBP α and diminishing its DNA binding capacity and by promoting cell proliferation. ATF3, an HBZ-binding protein, has bimodal functions in oncogenesis. On one hand, ATF3 activates p53 signaling and acts as a tumor suppressor^[91]. On the other hand, it promotes cancer cell proliferation^[49, 91]. Interestingly, HBZ inhibits the p53-enhancing function of ATF3, which is deleterious to ATL development, but does not hinder the cell proliferative function of ATF3 in ATL cells^[91]. Two independent studies have shown that HBZ also employs certain autocrine/paracrine pathways to enhance ATL cell proliferation^[92, 93]. HBZ suppresses the canonical Wnt pathway, but it enhances the proliferation and migration of ATL cells by increasing expression of the noncanonical Wnt5a^[92]. In addition, HBZ upregulates the expression of brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin receptor kinase B (TrkB), which further promotes ATL cell proliferation^[93]. HBZ-induced double-strand breaks (DSBs) are dependent on several microRNAs (miRNA) that are HBZ-inducible, such as miR17 and miR21^[94]. miR17 and miR21 target and suppress the expression of OBFC2A, a gene that encodes hSSB2, which is a single-stranded DNA-binding protein that prevents genomic instability^[94, 95]. Therefore, HBZ disrupts the genomic integrity of the host through the HBZ-microRNA-OBFC2A cascade^[95].

HBZ inhibits apoptosis and autophagy in HTLV-1 infected cells^[96-98]. A pro-apoptotic gene Bim is greatly suppressed by HBZ^[98]. FoxO3a is an important transcription factor that controls the expression of Bim^[98]. HBZ impairs the DNA-binding ability of FoxO3a and sequesters the inactive, phosphorylated FoxO3a in the nucleus by forming a ternary complex with FoxO3a and 14-3-3, thereby repressing the transactivation of

Bim and leading to the inhibition of apoptosis^[98]. Autophagy is a natural cellular digestion mechanism that removes unnecessary or damaged cellular components^[97, 99]. Recently, HBZ has been reported to activate the mTOR pathway by inhibiting growth arrest and DNA damage-inducible protein 34 (GADD34), a stress-induced GADD family protein that inhibits the mTOR pathway^[100]. In addition, autophagy and the mTOR pathway are inversely coupled; thus, mTOR activation caused by HBZ inhibits autophagy^[96]. Furthermore, it has been shown that among the HTLV-1 viral proteins, HBZ has the lowest immunogenicity because anti-HBZ antibodies can barely be detected in HTLV-1-infected individuals^[101]. A recent study suggests that the weak binding strength of HBZ epitopes to CTLs and the low expression of HBZ protein might greatly hinder the ability of the host to mount a successful anti-HBZ CTL response^[96]. It has been suggested that the low immunogenicity of HBZ likely helps the infected cells to escape immunosurveillance and contributes to HTLV-1-mediated oncogenesis.

The clinical diagnoses and therapies of HTLV-1 associated cancer

ATL is a rare T-cell malignancy caused by HTLV-1 infection. There are four subtypes of ATL (acute, lymphoma, chronic and smoldering) according to clinical manifestations, such as the white blood cell count in blood, serum lactate dehydrogenase (LDH) levels, organ involvement and blood calcium level^[102]. The clinical diagnosis of ATL is based on the anti-HTLV-1 antibody in the serum and the existence of a mature T-cell malignancy. To further confirm ATL, a Southern blot analysis is needed to identify the monoclonal integration of the HTLV-1 provirus into the target tumor cells. Recently, Shigeki Takemoto *et al.*^[103] reported that soluble CD30 (sCD30), a member of the tumor necrosis factor receptor superfamily, is a possible marker for ATL in HTLV-1 carriers. CD30 is expressed in lymphoma and even in normal cells^[104], and the soluble form of CD30 is produced by CD30-positive cells^[105]. Shigeki Takemoto *et al* found that ATL cells produced sCD30, and elevated levels of serum sCD30 correlated not only with the aggressiveness of the acute type of ATL but also with chemotherapy resistance^[106]. Furthermore, it has been suggested that the analysis of sCD30 levels may be useful for the prediction of overall survival of ATL patients, especially before allogeneic hematopoietic stem cell transplantation^[107]. Together, these studies have revealed that the increased circulating sCD30 is associated with the risk of developing ATL in asymptomatic HTLV-1 carriers.

The current treatment strategy for ATL varies from region to region. Additionally, the treatment is based on the clinical subtype^[108]. Strategies to combat HTLV-1 infections include peptide, recombinant protein, DNA, and viral vectors, and they ultimately lead to the development of various experimental vaccination and therapeutic regimens^[109]. However, the prognosis continues to be dismal for patients with aggressive-type ATL. To improve treatment outcomes, recent efforts have been focused on the combination of therapeutic modalities

ties, such as chemotherapy, antiviral therapy, allogeneic hematopoietic stem cell transplantation, and molecular targeted therapy, as well as the development of prognostic stratification and improved dosage and timing^[110].

Early chemotherapy is required for patients with aggressive ATL, including the acute and chronic types. To date, several chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and EPOCH (VP-16, prednisolone, vincristine, cyclophosphamide, doxorubicin) have been evaluated in patients with aggressive ATL^[111]. Since 1978, the JCOG-Lymphoma Study Group (JCOG-LSG) has played a particularly central role in the development of chemotherapy regimens for ATL patients. Modified (m)-LSG15 (VCAP-AMP-VECP), a new chemotherapy regimen, has replaced one course of VCAP-AMP-VECP from the original LSG15 regimen with intrathecal administration of methotrexate and prednisone as prophylaxis against central nervous system relapse. The original LSG15 regimen consists of sequential administration of vincristine, cyclophosphamide, doxorubicin, and prednisolone (VCAP); doxorubicin, rani-mustine, and prednisolone (AMP); and vindesine, etoposide, carboplatin, and prednisolone (VECP). Recently, the mLSG15 as an intensive chemotherapy has been recommended for aggressive ATL^[110]. It has been suggested that approximately 70% of ATL cases undergo clonal evolution, and genetic instability may contribute to genomic alterations^[112]. The existence of multiple clones with genomic instability is a crucial factor that renders ATL cells resistant to conventional chemotherapy. Even if a proportion of cells are killed by chemotherapy, new resistant clones are likely to emerge. For this reason, autologous HSCT (allo-HSCT) might be efficient in curing ATL patients by eliminating the HTLV-1-integrated recipient ATL clones through a strong immune response and subsequent replacement of the hematopoietic system with donor cells^[113]. Because type I interferons (IFNs) are critical effectors of the innate antiviral response, the combination of alpha interferon and zidovudine, an inhibitor of viral reverse transcriptase, has also been recommended as the standard first-line therapy for ATL.

Moreover, it has been reported that C-C chemokine receptor 4 (CCR4), a seven-transmembrane G protein-coupled receptor, may be used as a new target for ATL treatment. CCR4 is primarily expressed in regulatory T (Treg) cells and T helper type 2 (Th2) cells^[114], where it functions in inducing the homing of these leukocytes to sites of inflammation^[115, 116]. Treg impairs the host antitumor immunity and forms a favorable internal environment for tumor growth^[112]. CCR4 is highly expressed in ATL, and approximately 90% of HTLV-1-infected individuals are CCR4-positive^[117]. Remarkably, patients with CCR4-positive ATL have worse outcomes than those with CCR4-negative ATL. The results suggest that the upregulation of CCR4 plays a key role in the pathogenesis of ATL, likely through Treg functioning. Therefore, therapy with anti-CCR4 antibody may be a good choice. The first-in-class, man-made mogamulizumab, an anti-CCR4 monoclonal antibody, has been approved for the treatment of relapsed/refractory ATL

in Japan^[118].

Because the viral nonstructural proteins HBZ and Tax are critically involved in HTLV-1-mediated tumorigenesis, they may be used as targets for ATL treatment. Indeed, Sugata *et al*^[119] generated recombinant vaccine viruses (rVVs) expressing HBZ to determine the immunogenic potential of the viral protein. They found that rVV-expressing HBZ can induce specific CTL responses, and such vaccination partially protects mice from developing T-cell lymphoma. Furthermore, those authors also identified an HBZ peptide (amino acids 157-176) that could be used as a candidate for a peptide-based vaccine^[119, 120]. It has also been found that HTLV-1 infection can trigger chronic activation of the CTL response^[121]. Additionally, a high titer of anti-HTLV-1 antibodies directed against the Tax protein has been found^[122], indicating that Tax is the main immunogen during the viral infection^[116]. Previous studies have reported that the Tax vaccine protected against HTLV-1 infection in an animal model^[123]. Recently, a study confirmed that the Tax vaccine is effective in ATL patients^[124]. The current treatment strategies for ATL are summarized in Table 1.

Future direction

HTLV-1 is a critical human retrovirus that is linked to human cancer. Recently, viral proteins Tax and Rex of HTLV-1 have attracted a large amount of attention in clinical medicine. Based on their sequence homology, all Tax proteins possess a CBP/p300 binding region. These functional domains show some differences among Tax-1, Tax-2, Tax-3 and Tax-4. One of the major differences is related to the lysine residue at position 85 of Tax-1, which is necessary for it to bind CBP/p300^[51]. However, this residue is substituted by an arginine in Tax-2, Tax-3 and Tax-4^[125], indicating the functional differences between the Tax proteins. Further investigations of host factors altered in ATL may be helpful in identifying potential targets for effective therapies against this type of leukemia. Moreover, investigations on the subcellular localization of Tax proteins will provide useful information for addressing the mechanisms underlying the interaction of Tax with host factors. It has been shown that Tax oncoproteins perturb IFN production and signaling in HTLV-1-infected cells, and a better understanding of the molecular basis of this process would allow us to develop strategies to counteract Tax and re-establish the innate IFN response against the viral infection. For example, the agonists of both RIG-I and STING were found to have broad-spectrum antiviral effects^[126, 127]. In addition to Tax proteins, Rex plays an important role in HTLV pathogenesis. Further studies are still required to define its precise function.

HTLV-1 infection, a neglected and life-long disease, is currently still incurable and untreatable. The prevention of infection-associated cancers might be able to reduce a substantial proportion of human cancers. To prevent the spread of HTLV-1, a safe and effective vaccine is required. Although HBZ may be considered a useful target for ATL treatment, the efficiency of the recombinant vaccine virus expressing HBZ and HBZ peptide-based vaccine still needs to be further tested in human ATL^[119]. A previous study indicated that recom-

Table 1. Treatment strategies for adult T-cell leukemia/lymphoma.

Smoldering or favorable chronic-type ATL	Unfavorable chronic or acute-type ATL	Relapse or refractory ATL
<ul style="list-style-type: none"> . Asymptomatic patients: Watchful waiting . Symptomatic patients: Interferon-α (IFN-α)/zidovudine (AZT) or watchful waiting . Skin lesions: <ul style="list-style-type: none"> skin-directed therapy: topical steroids, ultraviolet light and radiation systemic therapy: steroids, oral retinoids or single agent chemotherapy 	<ul style="list-style-type: none"> . Chemotherapy: CHOP, EPOCH, LSG15 (VCAP-AMP-VECP) and mLSG15 . Allogeneic hematopoietic stem cell transplantation (allo-HSCT) . Interferon-α (IFN-α)/zidovudine(AZT) . VCAP-AMP-VECP+mogamulizumab 	<ul style="list-style-type: none"> . Allo-HSCT . Anti-CCR4 antibody . Vaccine: autologous dendritic cells with tax-peptide, HBZ . Promising targeted therapies and new agents: <ul style="list-style-type: none"> arsenic trioxide and IFNα, histone deacetylase and proteasome inhibitors, antiangiogenic therapy, bortezomib, survivin, β-catenin, syk, and lyn inhibitors, etc.

binant proteins derived from the immunogenic sequences of gp46 of the viral envelope had an effect on the induction of efficient immune responses^[109]. However, one of the limitations of antigenic peptides is their poor immunogenicity^[128]. To increase immune responses, peptide antigens can be potentiated with polymer-based nanoparticles, such as chitosan (CHT) and trimethylchitosan (TMC), as delivery adjuvants to overcome the limitation. It will be interesting to test whether the recombinant proteins of gp46 might be better candidates for vaccination against HTLV-1 infection^[129].

Despite the increase in new therapeutic options, treatment of ATL patients remains challenging. Some promising new agents for ATL are currently in translational research, and several are in clinical trials. Of note, the anti-CCR4 antibody mogamulizumab has been approved for refractory ATL. Moreover, CD30 is an activation marker of lymphocytes, and signaling through CD30 is associated with cell proliferation. A CD30-directed antibody-drug conjugate, brentuximab vedotin, has been assessed in a global phase III trial for ATL chemotherapy. In recent years, cancer immunotherapy has experienced rapid development. The chimeric antigen receptor (CAR)-modified T-cell has shown great promise in cancer treatment^[130]. The modified T-cell can be redirected to recognize tumor antigens through the expression of CAR. For example, the potency of CD19 CAR-T cells is unprecedented in the field of immunotherapy, particularly in the treatment of acute lymphoblastic leukemia (ALL) and B cell malignancies^[131, 132]. CAR-T might be employed in ATL therapy to recognize specific tumor antigens associated with HTLV-1, but further clinical trials are still needed. Additionally, lenalidomide, an immunomodulatory agent, is being tested in a phase II trial for relapsed aggressive ATL^[113]. There are additional new agents in ongoing ATL trials, including forodesine (a purine nucleoside phosphorylase inhibitor), pralatrexate (an anti-folate agent), and IL-2 fused with the diphtheria toxin targeting CD25. The application of several inhibitors, such as histone deacetylase inhibitors panobinostat (LBH589), romidepsin, depsi-peptide (HFR901228) and the proteasome

inhibitor bortezomib, has drawn greater attention in the field of ATL^[113, 133]. However, further studies are required to evaluate the efficacy of these inhibitors and prevent the occurrence of their side effects.

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