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Review

Molecular targeting for treatment of human T-lymphotropic virus type 1 infection

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ABSTRACT

Human T-cell lymphotropic virus type 1 (HTLV-1) infection is linked to adult T-cell leukemia-lymphoma (ATLL) and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and several other disorders. ATLL occurs in approximately 5% of the 15–20 million people infected by HTLV-1 in the world. In general, ATLL is resistant to chemotherapy, which underlines the need for new and effective therapeutic strategies. Previous studies highlighted the role of viral enzymes, responsible for viral replication, and regulatory proteins such as Tax and HBZ in the progression of HTLV-1-associated diseases. There are conflicting reports on the efficacy of current enzyme inhibitors, mainly developed against human immunodeficiency virus (HIV), for treatment of HTLV-1 infection. New treatment approaches including monoclonal antibodies show promising results and exert significant cytotoxic effects on ATLL cells. This manuscript reviews the recent developments in molecular targeting for treatment of HTLV-1 infection.

1. Introduction

Human T-lymphotropic virus type 1 (HTLV-1), firstly identified in 1980, belongs to the *Deltaretrovirus* genus of the *Retroviridae* family [1]. Inter-human transmission of HTLV-1 infection occurs most likely through breastfeeding, contaminated blood or blood products and sexual contact [2]. There are evidence demonstrating that exposure to the HTLV-1 infected cells allows transmission of cell-free viral particles to $CD4^+$ lymphocytes and other cell types [3,4]. However, cell-to-cell transmission and clonal proliferation of infected cells are more efficient in propagation of HTLV-1 virus (Fig. 1) [5,6].

HTLV-1 is endemic in certain areas of the world, including the south of Japan, the Caribbean islands, Africa, South America and parts of Iran [7–10]. There are 15–20 million infected people in the world, but the majority (more than 95%) remain asymptomatic (healthy carriers) [11]. Following a long period of clinical latency, 2–6% of HTLV-1 carriers may progress into ATLL, and a further 2–3% develop HAM/TSP symptoms [12–14]. Additionally, HTLV-1 infection is associated with several other disorders including uveitis, arthritis, alveolitis/bronchiectasis, dermatitis, and lymphadenitis [15–19].

A strong correlation between the viral load and clinical status of HTLV-1 infected individuals is observed [20,21]. However, the drugs developed for treating HIV infection are not effective for treating HTLV-1-associated diseases [22]. This manuscript highlights challenges and recent achievements in therapeutic targeting of viral functional enzymes, envelope glycoproteins, accessory proteins Tax and HBZ and the host cell signaling pathways modulated by HTLV-1 infection as therapeutic strategies for the patients.

1.1. Structure of the HTLV-1 genome

The HTLV-1 genome (8.5 kbp) includes structural genes, *gag*, *pol*, *pro*, *env*, and the pX region which are flanked by 5′ and 3′ long terminal repeat (LTR) sequences (Fig. 2). The 5′LTR serves as the main promoter for viral transcription. In ATLL patients, the 5′ LTR frequently undergoes deletion and methylation, while the 3′ LTR always remains intact [23–25]. Through a frameshifting mechanism, the *pro* and *pol* genes encode proteins Gag-Pro and Gag-Pro-Pol precursors. The Gag precursors encode the virion structural proteins (matrix (MA), capsid (CA), nucleocapsid (NC)), while proteolytic processing of Gag-Pro precursors

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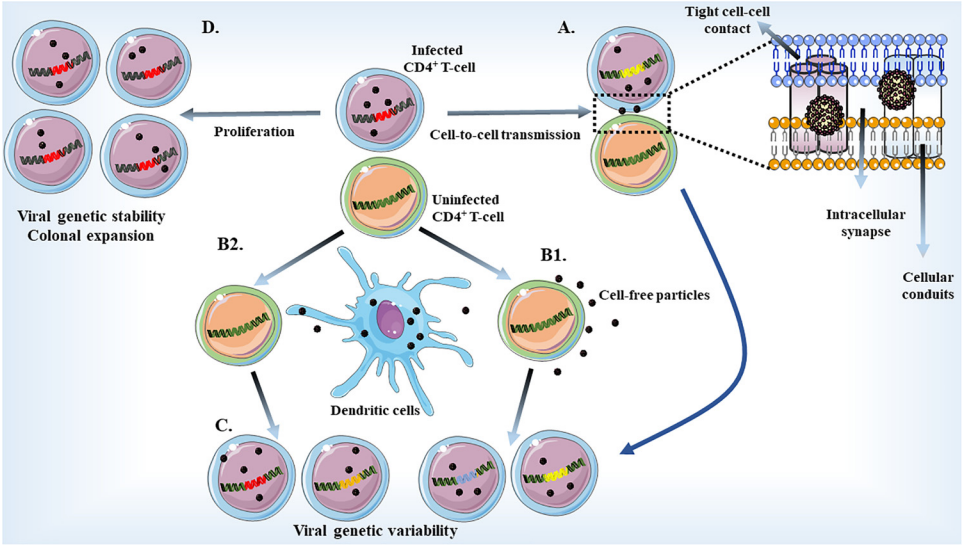

Fig. 1. Schematic representation of HTLV-1 amplification. (A.) The transmission of HTLV-1 infection is mediated by the cell-free virions that are transmitted through cellular conduits, the viral synapse or the viral biofilm. (B1 and B2) The cell-free HTLV-1 virions are poorly infectious for CD4 + T cells, they, however, can infect dendritic cells with high efficiency. (C.) The use of reverse transcriptase in the cell-associated viral transmission might lead to sequence variability. (D.) Cellular proliferation results in a large clonal amplification of infected cells, which are genetically stable. The clonal populations of Immortalized HTLV-1 infected cells with a same proviral integration site in the host genome are known as clonal expansion.

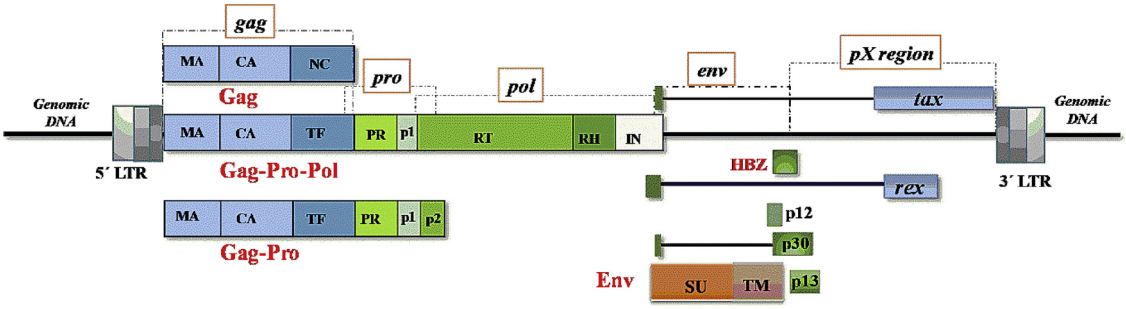

Fig. 2. HTLV-1 virus genome structure. The full-length messenger RNA encodes a large Gag-Pro-Pol precursor polyprotein, an alternatively spliced RNA encodes Env, and a pX region encodes the regulatory proteins (rex and tax).
HBZ = HTLV-1 bZIP-factor, LTR = long terminal repeat, MA = matrix, CA = capsid, NC = nucleocapsid, TF = transframe protein, PR = Protease, RT = Reverse transcriptase, IN = integrase, RH = RNase H, SU = Surface subunit, TM = Transmembrane region, Env = Envelope glycoprotein.

during maturation yields transframe protein (TF), protease (PR) and two smaller fragments (p1 and p2). The Gag-Pro-Pol precursors are processed into MA, CA, TF, PR, p1, reverse transcriptase (RT) and integrase (IN). The HTLV-1 genome also contains a *pX* region located between the *env* gene and the 3´ LTR. The *pX* region contains sequences for viral regulatory and accessory proteins, Tax, Rex, p12, p13, p30 and p21 and HTLV-1 bZIP factor (HBZ) which are involved in viral infection and pathogenicity [26].

1.2. Drug targets

In the absence of an effective vaccine against HTLV-1 infection [12], drugs are the only tool for treatment of the patients. Antiretroviral therapy does not eliminate viral reservoirs, but it does disrupt the virus life cycle and reduce the viral replication rate. Effective antiretroviral therapy for other retroviruses was reported to result in viral suppression, immunological recovery and improved the overall quality of life of the patients. Several steps in the retrovirus replication cycle are potential targets for antiretroviral therapy. These steps can be divided into the entry and post-entry steps. The viral envelope glycoproteins and their receptors are involved in viral entry. The success for inhibition of human immunodeficiency virus (HIV) entry suggests that envelope glycoproteins of HTLV-1 could also be targets for antiviral therapy.

All human retroviruses, including HTLV-1 and HIV, encode three enzymes, PR, RT and IN, required for viral replication in the post-entry steps [27]. These key enzymes are attractive targets for antiviral therapy and have been successfully targeted in HIV-1 infection. Based on the successful application of such inhibitors in HIV-1 infection therapy, the enzymes involved in HTLV-1 replication are also considered as the primary targets for drug design [12,28]. Additionally, accessory proteins including Tax and HBZ might also serve as targets for antiretroviral chemotherapy.

The host cell signaling pathways modulated by HTLV-1 infection are also considered as drug targets. The NF-κB pathway is chronically activated in HTLV-1 infected cells and inhibition of NF-κB induces apoptosis of HTLV-1-infected T-cells [29]. Cellular transformation leads to changes in the activity of enzymes involved in DNA replication and repair as well as chromatin remodeling. Histone deacetylases (HDACs) inhibitors are effective in patients with cutaneous T-cell lymphoma (CTCL) and T-cell lymphoma [30].

2. Targeting HTLV-1 envelope glycoproteins

The growing research on the pathogenesis of HTLV-1 revealed it has the potential to infect $CD4^+$ T-cells as the main targets as well as a broad range of other cells, from $CD8^+$ T-cells, B-lymphocytes, fibroblasts, endothelial cells, myeloid cells to other mammalian cells. This wide variety of target cells is in part due to the ability of the virally encoded envelope glycoprotein (Env) to bind various membrane-associated receptors on the target cells [31].

HTLV-I Env is synthesized as a precursor gp6l protein which is proteolytically cleaved into the gp46 and gp21 glycoproteins. The gp46 surface subunit (SU) and gp21, the transmembrane region (TM), are non-covalently linked with each other [32]. Similar to their HIV counterparts, it is believed the SU and TM of HTLV-1 play a crucial role during the entry process [33]. Once HTLV-1 has attached to the host

cell membrane, the fusion process initiates through sequential events between the SU and the cell membrane receptors, including the glucose transporter (GLUT1), heparin sulfate proteoglycan (HSPG), and the vascular endothelial growth factor-165 receptor neuropilin-1 (NRP-1). The HTLV-1 SU forms complexes with the HSPGs, NRP-1, and GLUT1 to trigger fusion of the retroviral and cellular membranes, which allows releasing the retroviral capsid core into the cytoplasm of the host cell [12].

Several HIV-1 inhibitors have been described to inhibit HIV entry into target cells, some of which are FDA approved (enfuvirtide and maraviroc) or in various stages of development. For detailed information about cell binding and entry process of HIV-1 and its inhibitors, readers are referred to the reviews of Robert W. Doms [34,35]. There are no approved therapeutic agents targeting the HTLV-1 entry process; however, it was reported that the synthetic peptides, capable of interfering with the conformational changes of TM subunits, potently inhibit Env-mediated membrane fusion and HTLV-1 entry into host cells [36–38]. For example, Mirsaliotis et al. reported that synthetic peptides based on the leash and α-helical region (LHR) of the gp21 act as potent inhibitors of membrane fusion and HTLV-1 entry [37]. Sulfated polysaccharides such as heparin have also inhibitory activities against several retroviruses. Chondroitin sulfate type E (CSE) and heparin exhibited anti-HTLV-1 activity [39,40]. CSE interacts directly with recombinant Env proteins of HTLV-1 at the C-terminal portion of SU and blocks the virus binding to a human T cell line (MOLT-4 cells) [39].

3. Targeting HTLV-1 enzymes

3.1. Reverse transcriptase

Reverse transcription of the retroviral RNA occurs after retroviral fusion with the cellular membranes and entry of the retroviral core components into the cytoplasm of the host cell. It is a unique process that is responsible for the conversion of single-stranded RNA (ssRNA) to double-strand DNA (dsDNA) [41,42]. Reverse transcription is catalyzed by the multifunctional, retroviral-encoded reverse transcriptase (RT) enzyme [43,44]. The enzyme, firstly discovered in 1970 by Temin and Baltimore, has two enzymatic functions, RNA-dependent DNA polymerase as well as ribonuclease H (RNase H) [41,45]. The latter is responsible for the hydrolysis of RNA in an RNA/DNA duplex. Long interspersed element-1 (LINE-1) reverse transcriptase and telomerase are eukaryotic enzymes with similar activity [46]. Despite the results of some *in vitro* studies [47,48], no change was observed in telomerase activity or telomere length of the patients receiving darunavir/ritonavir treatment for three years in the MONET trial [49].

The current knowledge on the mechanism of action and also inhibition of retroviral RTs is based on biochemical studies and crystallography of the HIV RT. HIV-1 RT is the target for two distinct major classes of enzyme inhibitors: the nucleoside/nucleotide RT inhibitors (NRTIs) and the non-nucleoside RT inhibitors (NNRTIs). The NRTIs are nucleoside analogs that need to be converted to their triphosphate derivatives by host cell kinases before exerting an antiretroviral effect. NRTIs compete with endogenous dNTP in binding to the RT catalytic site and interfere directly with the polymerization process. Lack of a functional 3′-hydroxyl group in the ribose ring of the NRTIs prevents the formation of a phosphodiester bond between the NRTI and the subsequent nucleotide, resulting in chain termination during dsDNA synthesis [50,51]. NNRTIs interact with an allosteric binding site located a short distance away from the polymerase catalytic site of HIV-1 RT. Binding of an NNRTI to the allosteric pocket inhibits the catalysis by altering the structural conformation [42,52–54].

To date, there are neither specific inhibitors nor a published crystal structures for HTLV-1 RT. Fig. 3 depicts the sequence alignment of HTLV-1 and HIV-1 RTs. These enzymes share ~25% sequence identity and ~45% similarity. The pairwise alignment analysis of HTLV-1 RT and HIV-1 RT indicated the YMDD and LPQG motifs are highly conserved among retroviruses and play an essential role in polymerase catalytic activity [55,56]. However, most of the residues in the HIV-1 NNRTI pocket are different from HTLV-1. As a result, The NNRTIs developed for HIV-1, such as nevirapine (ART), have very low or no activity against HTLV-1 RT [56].

Currently there are several FDA-approved nucleoside analogues including zidovudine (AZT), emtricitabine (Emtriva, FTC), didanosine (Videx, ddI), lamivudine (Epivir, 3TC), stavudine (Zerit, d4T), abacavir (Ziagen, ABC), zalcitabine (Hivid, ddC), and tenofovir (Viread, TDF). Evidence indicates that a limited number of HIV-1 NRTIs can inhibit viral replication in HTLV-1 infected cells in single or in combination therapy [57–59]. AZT, a pyrimidine nucleoside analog, can efficiently inhibit HTLV-1 transmission to target cells with the half maximal inhibitory concentration (IC_{50}) of 0.11-0.45 μM [56,60,61]. It was also shown that the active phosphate forms of AZT, ddI (IC_{50} = 0.03 μM), ddC (IC_{50} = 0.27-0.87 μM), and d4T (IC_{50} = 0.7–14.5 μM) could partially inhibit HTLV-1 RT function [56,58,62]. TDF inhibits the enzymatic activity of HTLV-1 RT at lower concentrations (IC_{50} = 0.005-0.35 μM) than AZT [59,63]. Both TDF and AZT were capable of blocking primary infection in human peripheral blood mononuclear cell-NOG (huPBMC-NOG) mice. Taylor et al observed a 10-fold reduction in HTLV-1 viral load during treatment with 3TC in HAM/TSP patients [64]. Conversely, there are reports on HTLV-1 RT resistance to 3TC; therefore, it is unlikely to have direct antiretroviral efficacy in HTLV-1-infected patients [56,65,66]. In the co-culture of PBMC cells with MT-2 cells, cyclic nucleoside phosphonate (PCOAN) compounds inhibited RT activity and also the growth of HTLV-1 infected cells 100–200 times more effectively than TDF [67]. Half maximal effective concentrations (EC_{50}) against HTLV-1 in PBMC cells for PCOAN compounds were in the range of 0.3-0.61 μM, whereas the EC_{50} values for TDF and AZT were 66.5 and < 0.1 μM, respectively.

3.2. Integrase

After reverse transcription of viral genomic RNA and dsDNA synthesis, viral DNA is incorporated into the genome of the host cell by the retroviral enzyme integrase (IN) [68]. This integrated DNA copy, called a provirus, acts as the template for viral RNA production [69]. The integration proceeds through two steps; during the first step, called 3′ processing, three nucleotides are cleaved from the 3′ ends of LTRs by IN to reveal new 3′-hydroxyl (3′ OH) groups. In the second step, strand transfer, these nucleophilic 3′ OH groups attack the phosphodiester bond of the cellular DNA. Then, integrase catalyzes the joining of the two viral DNA ends into the host DNA through a one-step transesterification reaction. Finally, the gaps at the site of insertion on each target strand are filled in and repaired by host cell enzymes [70,71].

Retroviral integrases contain three structural domains, the N-terminal domain (NTD), containing a highly conserved HHCC (His-His-Cys-Cys) motif, the catalytic core domain (CCD) with the catalytic triad of acidic amino acids (DDE motif) and the C-terminal domain (CTD) which binds dsDNA. The NTD includes a zinc-finger motif and binding of zinc stabilizes the folding of this domain and increases its enzymatic activity. The CCD contains a triad of acidic residues that bind Mn^{2+} or Mg^{2+}. Mutation of any of these three acidic amino acids abolishes catalytic activity of the enzyme [72].

Integrase has no counterpart in human cells and could be a promising target for antiretroviral drug development. Some HIV-1 IN inhibitors were tested *in vitro*, *ex vivo* and *in vivo* on the HTLV-1 enzyme [73–75]. The two main classes of HIV-1 IN inhibitors are styrylquinolines (SQLs) and diketo acids (DKAs). SQLs and DKAs were tested *in vitro* in an HTLV-1 strand-transfer assay and *ex vivo* by infection of fresh peripheral blood lymphocytes with lethally irradiated HTLV-1-positive cells. All compounds active *in vitro* could reduce cell proliferation *ex vivo* at low concentrations. They also dramatically decreased both proviral loads and the number of integration events [73].

Raltegravir was the first IN inhibitor approved for clinical use in the

Fig. 3. Sequence alignment of HTLV-1 and HIV-1 RTs. The YMDD and LPQG motifs are boxed in black. The residues involved in NNRTI binding are marked by asterisks.

treatment of HIV-1 infection. It targets the strand transfer step of purified HIV-1 IN *in vitro* with an IC_{50} value of 2–7 nM. It also inhibited HTLV-1 transmission in lymphoid and non-lymphoid cells as well as HTLV-1 immortalization of human peripheral blood mononuclear cells (PBMCs) (EC_{50} 35 nM) [75]. However, no significant decrease in proviral load was observed in the HTLV-1 carriers after six months treatment with the recommended dose for HIV treatment (400 mg twice daily). This result may be explained by the fact that the clonal expansion by mitotic replication of HTLV-1 infected cells is the dominant mechanism of viral propagation in the chronic carriers [74]. MK-2048, as a DKAs derivative, also inhibited cell-free and cell-to-cell transmission of HTLV-1 in lymphoid and non-lymphoid cells with an EC_{50} value of 1 nM [75].

3.3. Protease

HTLV-1 encodes an aspartic PR that processes viral Gag and Gag-(Pro)-Pol polyproteins during maturation. The substrate binding site of the enzyme is mainly made up from residues located at three different regions, C-terminal region, flap region and active site region as shown in Fig. 4. The active site of HTLV-1 PR includes two aspartic acid residues (Asp32, 36) that participate in the hydrolysis of polyproteins through an acid-base mechanism. Similar to other retroviral PRs, HTLV-1 PR is critical for virus replication. Several PR inhibitors are in clinical use for the treatment of acquired immune deficiency syndrome (AIDS). The inhibitors of HIV-1 PR, *i.e.*, saquinavir, indinavir, nelfinavir, atazanavir, darunavir, ritonavir and lopinavir, contain hydroxyethylamine or hydroxyl ethylene moieties that act as transition state analogs.

The 3D structure of HTLV-I PR is similar to HIV-1 homodimeric aspartyl PR [76,77] and potent HIV-1 PR inhibitors, such as compounds KNI-727, KNI-764, and ritonavir were tested as HTLV-1 PR inhibitors. Unfortunately, these compounds were ineffective against HTLV-I PR, even though, some other KNI compounds showed partial activity (Table 1). Ritonavir displayed anti-leukemic activity against ATLL cells *ex vivo* [78], however, this was mainly due to inhibition of NF-κB activity, rather than inhibition of the HTLV-1 PR [73].

Recently, the crystal structure of HTLV-1 PR in complex with an HIV-1 PR inhibitor indinavir (IDV) was resolved (Protein data bank code 3WSJ) [76]. Comparing the crystal structures revealed highly similar folding, even though HTLV-1 and HIV-1 PRs only have 26% amino acid sequence identity (38% similarity). The sequence alignment of HIV-1 and HTLV-1 PRs is shown in Fig. 4. The HIV-1 PR coding sequence has only 99 amino acids per chain, whereas the HTLV-1 PR is substantially longer with 116 residues [79].

The investigation of HTLV-1 PR inhibitors is still in its early stages. Studies indicated that the HIV-1 PR inhibitors currently used in AIDS therapy are not highly effective against HTLV-1 PR. The active site regions of HTLV-1 and HIV-1 PRs differ only in one residue (Asp30 in HIV-1 is substituted by Met37 in HTLV-1 PR), but most of the amino acids of the C-terminal and flap regions are different in both enzymes. Thus, differences in the binding site residues of the PR enzymes result in differences in susceptibility to inhibitors.

Table 1, as an updated version of the table previously published [27], summarizes inhibitors of HTLV-1 PR having K_i (or IC_{50}) values of less than 500 nM; these compounds can be considered as lead compounds for further investigations. Except for the MES13-099 and DMP-323 ($ki > 10\,\mu M$), the compounds are peptides or modified peptides. JG-365 (Fig. 5) a heptapeptide inhibitor, is the best inhibitor of HTLV-1 PR reported to date with a K_i of 6 nM [80].

4. Targeting tax

Tax is a 40 kDa phosphoprotein encoded by an open reading frame in the pX region of the HTLV-1 genome. it is believed that Tax plays a central role in T-cell transformation through enabling the cells to overcome apoptosis and senescence [81,82]. Tax increases viral replication by transactivation of the HTLV-1 promoter in the 5´ LTR region. It also modulates the transcription of numerous target genes *via* activating the NF-κB pathway and inducing IκB-α degradation. Tax interacts with many host cell proteins involved in cell cycle, cell proliferation, p53 dependent apoptosis, and DNA repair [83].

Due to its role in transformation, Tax was considered as a potential therapeutic target in ATLL. Tax expression plays an important role in initiating cell transformation but it is not essential afterward, and the HBZ protein drives the maintenance of the transformed cells [83,84]. As a result, Tax transcripts are detected in only 40% of patients with ATLL. Thus, the therapeutic benefit of Tax targeting in HTLV-1-associated diseases may be limited.

A synthetic retinoid, ST1926, was reported to downregulate the oncoprotein Tax, upregulates p53 protein, and induces cell cycle arrest as well as apoptosis in HTLV-1-infected cell lines [85,86]. Cyclosporin A, a natural cyclic polypeptide from an extract of soil fungi, is a powerful immunosuppressant that inhibits cytokine production and T cell activation [87]. Ozaki et al. observed that cyclosporine A inhibited the production of Tax in HTLV-1 infected T-cells and Tax cDNA transfected cells [88]. Niclosamide, an anti-helminthic drug that is FDA approved for the treatment of tapeworms, induced degradation of the Tax protein in the proteasome and subsequently inhibited the viral gene transcription of HTLV-1 [89].

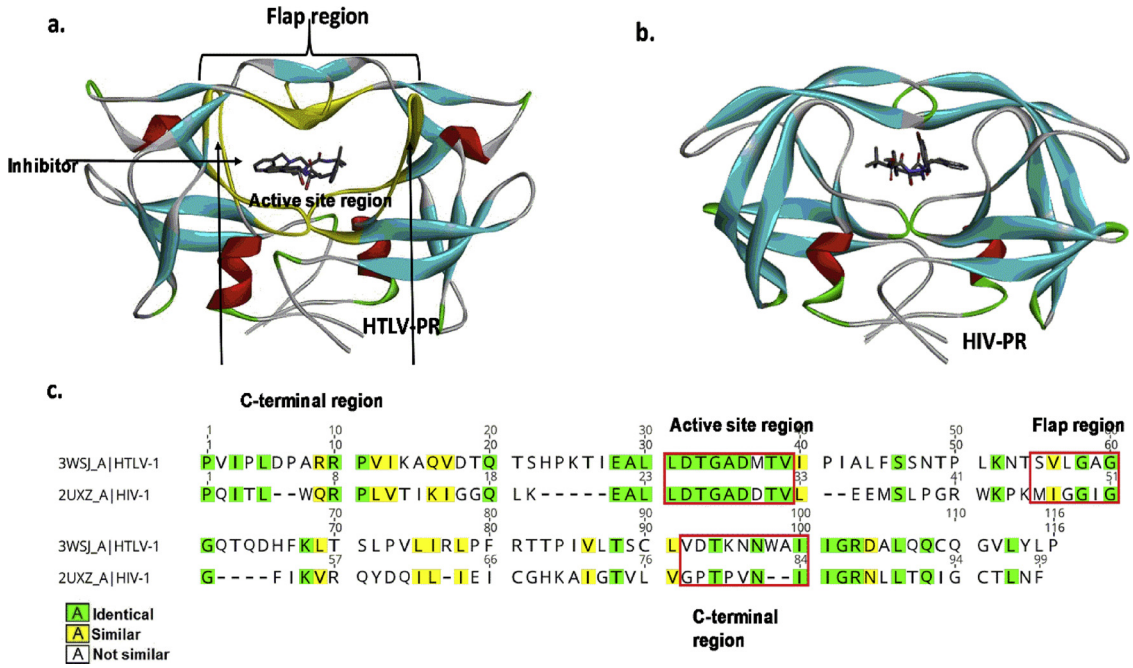

Fig. 4. Protease protein structure and sequence. The crystal structure of HTLV-1 (a.) and HIV-1 (b.) proteases. Amino acid sequence alignment of HIV-1 and HTLV-1 proteases sequences (c.) showing identical (green) and similar (yellow) residues.

Table 1
Inhibitors of HTLV-1 PR with Ki (or IC_{50}) values of less than 500 nM.

Inhibitor	Ki (nM)	Ref.
MES13-099	240	[57]
Boc-Val-Val-Phe-(PC)Phe-Val-Val-NH2	80	[58]
Ala-Pro-Gln-Val-Sta-Val-Met-His-Pro	50	[57]
Ac-Ser-Leu-Asn-Phe[HEA]-Pro-Ile-Val-OMe (JG-365)	6	[59,60]
Ac-Ile-Ile-Apns-Dmt-Ile-Phe-NH2 (KNI-10192)	95	[61]
Ala-Pro-Gln-Val-Sta-Val-Met-His-Pro[a]	50	[58,62]
Ac-Phg-Tle-Apns-Dmt-Ile-Gln-NH2 (KNI-10221)	84	[61]
PrCO-Phg-Tle-Apns-Dmt-HN i Pe (KNI-10635)	74	[61]
Pro-Val-Ile-HEA[S-Ibu,R-OH]-Pro-NH-CH2-C6-H4I	80	[61]
KNI-10127	353[b]	[63]
KNI-10161	159[b]	[61]
KNI-10162	152[b]	[64]
KNI-10166	88[b]	[61]
KNI-10247	144[b]	[61]

Abbreviations used in the peptide structuresHEA, [CH(OH)CH2; N] hydroxyethylamine; PC, phosphinic acid isostere; Sta, statine; -r-, reduced peptide bond; OMe, O-methyl; HEA, hydroxyethylamine; Ibu, isobutyl; Apns, allophenylnorstatine; Dmt, (R)-5,5-dimethyl-1,3, thiazolidine 4-arboxylate; Tle, L-tert-leucine; PrCO, cyclopropylmethyl; iPe, isopentyl.

[a] Statine-containing inhibitors based on naturally occurring HTLV-1 cleavage sites.

[b] These are IC50 values.

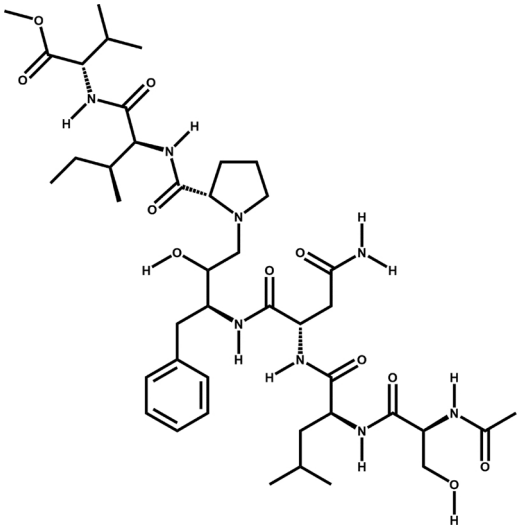

Fig. 5. Structure of the heptapeptide inhibitor JG-365.

5. Targeting host cell surface proteins using monoclonal antibodies

Several surface proteins were targeted on the ATLL cells using monoclonal antibodies. Humanized monoclonal antibodies directed to CD52/Campath-1H (alemtuzumab) and CD2 (siplizumab) have shown activity in a murine model of ATLL or lymphoma [90]. The first clinical trial was conducted by Waldmann et al. to evaluate the efficacy of the anti-CD52 antibody alemtuzumab in 19 patients with ATLL. The outcome was two complete and four partial responses with the duration of the responses from 9 weeks to more than three years [91].

CD25 is an alpha chain of the human interleukin-2 receptor (also called the TAC antigen), which is expressed on ATLL cells [91,92] and cells infected with HTLV-1. Therefore, treatment with blocking monoclonal antibodies concomitant with anti-cancer agents had encouraging results [59,93].

Monoclonal antibodies against interleukin-15 or its receptor also suppressed the spontaneous proliferation of PBMCs from patients with HTLV-I-associated myelopathy [94].

A24 is a neutralizing monoclonal antibody against the transferrin receptor that induces internalization of the receptor and therefore blocks iron entry into the cells. Iron deficiency induces cell-cycle arrest and apoptotic processes in ATLL cell lines and primary ATLL cells [94].

The CC chemokine receptor 4 (CCR4) is a G-protein-coupled receptor which is preferentially expressed on the surface of T-helper 2 and regulatory T-cells. Many T-cell lymphomas such as ATLL display high CCR4 expression. Thus, it is a potential target for antibody-based therapy in the treatment of T-cell neoplasms, especially in ATLL. Mogamulizumab (KW-0761) is an anti-CCR4 monoclonal antibody with a defucosylated Fc region, which showed antitumor activity [95,96] and improvement in overall survival of the ATLL patients [97].

6. Targeting host cell intracellular proteins

6.1. NF-κB inhibitors

The NF-κB pathway is chronically activated in HTLV-1-transformed cell lines and freshly isolated ATLL cells, even in the presence of low Tax expression levels. As discussed earlier, this transcription factor plays a crucial role in the protection of the leukemia cells from apoptosis and also their proliferation [81,82]. Therefore, its signaling pathway was targeted using the inhibitors Bay 11-7082 [98], (DHMEQ: a 5-hydroxymethyl derivative of epoxyquinomicin C) and indole-3-carbinol [99].

Treatment with Bay 11-7082 induced apoptosis of HTLV-1-infected T-cells and prevented primary tumor growth and leukemic infiltration in various organs in an *in vivo* mouse model of ATLL [29]. DHMEQ induced apoptosis in primary ATLL cells and cell lines derived from patients with ATL. It also selectively targeted HTLV-1–infected cells *in vitro*, resulting in a decreased number of infected cells [99]. Indole-3-carbinol, a naturally occurring component of Brassica vegetables, is also suggested as a potentially useful therapeutic agent for ATLL patients [99].

6.2. Histone deacetylase inhibitors

As an epigenetic effector, histone deacetylases (HDACs) catalyze deacetylation of the lysine residues in histone amino termini, leading to the condensation of chromatin and repression of transcription. Studies indicated that the transformed cells might be more sensitive to HDAC inhibitors compared with normal cells [100,101]. Valproate (2-*n*-propylpentanoic acid) is an HDAC inhibitor and stimulates histone hyperacetylation and activation of the HTLV-1 5´ LTR promoter. In 2011, Belrose and colleagues investigated the effect of valproate on Tax production in cultured lymphocytes from HTLV-1 carriers. They reported valproate enhanced and prolonged Tax-mRNA expression during short-term culture of HTLV-1-infected cells. Since TAX is the immunodominant protein of HTLV-1, prolonged Tax expression may expose the latently infected cells to the host immune system [102]. Other studies, however, showed that some HDAC inhibitors induce cell differentiation, cell-cycle arrest and apoptosis in a variety of transformed cells *in vitro* and *in vivo* [103]. Romidepsin (depsipeptide, FK228, FR901228), a cyclic peptide class of HDAC inhibitors, was effective in patients with CTCL and T-cell lymphoma [30]. It could suppress the expression of NF-κB and AP-1 and induced apoptosis of HTLV-1-infected T-cell lines and primary ATLL cells. Additionally, *in vivo* use of romidepsin partly inhibited the growth of tumors of HTLV-1-infected T cells transplanted subcutaneously in severe combined immunodeficiency (SCID) mice [104,105]. Several other HDAC inhibitors such as vorinostat (SAHA), panobinostat (LBH589) and MS-275 have also shown promising results in preclinical and/or clinical studies against T-cell malignancies. Vorinostat and romidepsin are FDA-approved drugs for the treatment of refractory and relapsed CTCL. LBH589 induced apoptosis in ATLL-related cell lines, primary ATLL cells and reduced the size of tumors inoculated in SCID mice [106]. These findings suggest that several mechanisms may be involved in the effects resulting from treatment with HDAC inhibitors.

6.3. DNA replication and repair inhibitors

Targeting of DNA replication and repair processes has been proposed as a promising strategy for cancer therapy [107,108]. Recent studies indicate that HTLV-1-derived cell lines and Tax-expressing cells exhibit defects in both DNA replication and DNA damage response [109]. Moreover, it has been shown that Werner syndrome ATP-dependent helicases (WRN), which play important roles in replication fork progression and participate in DNA repair, are highly expressed and it is essential for the survival of ATLL cells [110,111]. The WRN inhibitors NSC 19630 and NSC 617145 induce cell cycle arrest and apoptosis in the HTLV-1-transformed and patient-derived cells [112].

Poly (ADP-ribose) polymerase (PARP) plays a key role in some cellular processes including DNA repair [113]. A PARP inhibitor, PJ-34, was shown to induce cell cycle arrest in various human cancers, including acute myeloid leukemia (AML). Bai et al. demonstrated that PJ-34 can also activate p53 and caspase-3-dependent apoptosis in HTLV-I-transformed and ATLL-derived cell lines [114].

6.4. Proteasome inhibitors

Bortezomib (PS-341), a peptidyl boronic acid inhibitor of the proteasome, inhibits the function of the 26S proteasome complex [115]. In ATLL cells, bortezomib inhibits the degradation of IκB-α and prevents translocation of the NF-κB protein into the nucleus and transcription of its target genes. This results in suppression of the NF-κB signaling pathway and induction of ATLL cell death [116,117]. However, further investigations are required to clarify clinical utility of such inhibitors in patients with ATLL.

6.5. Survivin inhibitors

Survivin plays an important role in oncogenesis [118] and surviving inhibitor, YM155, suppresses cell proliferation and induces apoptosis in ATLL cells [119,120]. In addition, the combination of YM155 with anti-CD52 monoclonal antibodies was shown to increase survival in a murine model of human ATLL [121].

7. Combination therapies

The current treatment strategies for HTLV-1-related diseases are based on classical anti-cancer and anti-HIV drugs; however, none of these are specific for HTLV-1. It has been demonstrated that type I interferons (IFNs) are effective against HTLV-1 infection [122–127] *via* activating several genes with antiretroviral activity [125,128]. They also have an antiproliferative function and can block the cell growth of tumor cells [129]. Combination of AZT/IFN generated complete or partial responses in 11 of 19 ATLL patients, an overall response rate of 58 percent including five complete and six partial remissions. [93]. Hermine et al. also reported that AZT combined with IFN induces a rapid and durable response in 5 ATLL patients [130]. In 2010, Bazarbachi et al. published a meta-analysis on the use of AZT/IFN-α combinations in 254 patients with ATLL (116 acute ATLL, 18 chronic ATLL, 11 smoldering ATLL, and 100 ATLL lymphomas). They concluded that AZT combined with IFN-α had a major impact on overall survival of the patients with ATLL, with a 5-year overall survival of 46% for the whole population. This combination protocol was also recommended as the first-line therapy for the leukemic subtypes of ATLL [122]. Since AZT is not a specific and potent HTLV-1 RT inhibitor [60,131], it seems that the success rate of this protocol can be improved by the development of highly potent drugs against HTLV-1 reverse transcriptase.

Arsenic trioxide (AS) combined with IFN-α synergize to induce cell cycle inhibition and apoptosis in cells infected with HTLV-1 and in the malignant cells of ATLL. These events possibly occur *via* inactivation of the NF-κB pathway through up-regulation and stabilization of IκB-α as well as down-regulation and increasing degradation of Tax [132,133]. The results of phase II clinical trials using AS/INF-α combination therapy in 7 patients with a history of relapsed and refractory ATLL showed one complete remission and three partial remissions, and one patient was still disease-free after seven years.

In a recent prospective phase II study, the efficacy and safety of AZT/INF-α/AS combination therapy was investigated in 10 diagnosed chronic ATLL patients. An impressive 100% response rate was observed; out of the ten patients, seven had complete remission, two had complete remission but with 5% circulating atypical lymphocytes, and

one partial response was observed with mild hematologic side effects. However, in the ultimately cured mice, blood cell counts remained highly abnormal when treatment with IFN-α/As_2O_3 was discontinued [134,135].

8. Conclusions

Despite discovery of the virus nearly 40 years ago, unlike HIV, there is still no effective treatment for HTLV-1-associated diseases. This resulted from several factors including structural differences in enzymes leading to HTLV-1 resistance to HIV drugs and differences in rout of viral dissemination. Limited, but promising responses were achieved by combining the HIV drug AZT with INF-α. The limitations of this approach may result from the low efficacy of AZT against HTLV-1 RT, which can be addressed by the development of potent inhibitors against HTLV-1 enzymes. Simultaneous targeting viral enzymes with the signaling pathways involved in clonal proliferation of the infected cells should be considered as a selective treatment for the diseases caused by HTLV-1 infection.

Conflict of interest

The authors have no financial conflicts of interest.

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