HTLV-1: The Fundamental Proteins for ATL
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Abstract

HTLV-1 is an enveloped delta retrovirus common in rural areas with neglected health care systems. About 10 million people are affected globally. It is most often diagnosed in areas near the equator. It is mostly spread through blood transfusions but can also be spread by breastfeeding and unprotected sex. Breastfeeding has an infection rate of only around 5%. Unprotected sex has the highest probability of resulting in HTLV-1 infection. While sharing needles will lead to infection, plasma and industrial blood products can not transmit the virus. It is the sole cause of ATL (Adult T-Cell Leukemia). Symptoms of ATL are swollen lymph nodes, enlarged livers and/or spleen, and rashes. To test for HTLV-1, doctors use: Enzyme Linked Immunoassay, Particle Agglutination Assay, Western Blotting, Immunofluorescence Assay, Radioimmunoprecipitation Assay, and PCR. The Western Blot test is the most commonly used test.. This cancer has a <50% survival rate as it is not curable yet. There are many proteins involved in this pathogenesis. Each of these proteins have their own unique way of contributing to leukemogenesis or the life cycle of the virus. Tax is a transactivator and can mutate cells, Rex is essential for early stages, regulates expression and carries important viral messages, HBZ encodes many necessary accessory genes and is key to leukemogenesis. Studying HTLV-1 is important because it can lead to treatments and cures for this cancer. This review is meant to focus on HTLV-1 genes Tax, Rex, and HBZ and other associated proteins that can play a role in leukemogenesis, specifically ATL, and T-Cell Dysfunction.

Overview

The enveloped retrovirus HTLV-1 infects monocytes, dendritic cells, B-cells, monocytes, and T-cells (Eusebio-Ponce et al., 2019). However, the virus can only transform T-cells; specifically CD4+ T Lymphocytes, which help the immune system adapt to pathogens, possibly resulting in ATL (Eusebio-Ponce et al., 2019). 10% of carriers develop this form of leukemia (Eusebio-Ponce et al., 2019). Like most retroviruses, a viral particle attaches to a T-cell receptor through the viral envelope, entering through fusion (Eusebio-Ponce et al., 2019). The capsid then uncoats and releases RNA into the cell cytoplasm (Eusebio-Ponce et al., 2019). Most patients are asymptomatic as HTLV-1 maintains its copy number (number of copies of a plasmid) during chronic infection (Matsuo et al., 2022). For copy number to remain consistent, the virus utilizes clonal expansion (production of new cells) coupled with a persistence of HTLV-1 infected T-cells (Matsuo et al., 2022). This virus contains regulatory genes (tax and rex), accessory genes (P12^I , P13^{II}, P30^{II} and HBZ), and structural genes, found in all viruses (gag, pol, env) (Matsuo et al., 2022). Proteins from this virus are coded for in the PX region, which is between 3'LTR and ENV. PX-I and PX-II are open reading frames which code for genes P12^I , P13^{II}, and P30^{II} (Matsuo et al., 2022). PX-III and PX-IV code for genes tax and rex (Matsuo et al., 2022). The PX region additionally codes for the HTLV-1 Bzip factor (HBZ) Proteins are transcribed in antisense direction (3' to 5') (Matsuo et al., 2022). There are many components
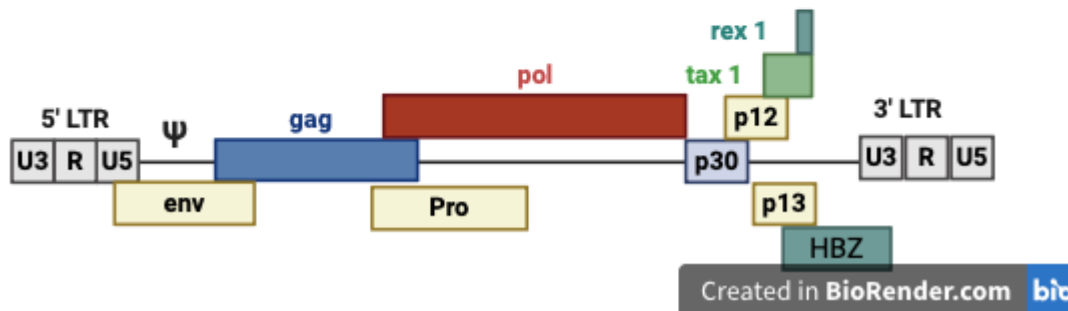
to this retrovirus, all equally important.
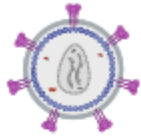
Figure #1 shows the viral structure of HTLV-1.

This figure was created with biorender.

Tax Gene

Tax is a trans activator of HTLV-1 and important for the virus's replication and pathogenesis (Currer et al., 2012). Trans-activators are genes which amplify virus transcription, allowing signaling pathways to work faster (Currer et al., 2012). Tax is highly oncogenic, meaning it can easily cause cancer (Currer et al., 2012). Studies have shown that ATL or other tumors will form in mice when Tax is injected into them (Takeo-Ohsugi 2019). However, this oncoprotein doesn't have a significant role in direct leukemogenesis (Takeo-Ohsugi 2019). Tax is very immunogenic, meaning it is easy for the body to activate an immune response against it (Robert-Currer et al., 2012). Therefore, it is often suppressed in vivo of infected cells (Robert-Currer et al., 2012). HTLV-1 has low transcription rates for Tax so it will be able to infect cells for long periods of time without a significant immune response (Robert-Currer et al., 2012). Despite this, Tax allows the virus to spread so it will be able to infect CD4+ T cells and eventually cause ATL (Charles-RM-Bangham et al., 2015). Since it is a transactivator it is able to activate many oncogenic pathways by activating the HTLV-1 LTR promoter which allows for the transcription of the virus (Charles-RM-Bangham et al., 2015). It prompts the CD4+ T cells to produce the chemokine CCL22 (Charles-RM-Bangham et al., 2015). This chemokine fosters a high frequency of regulatory CD4+ T cells (Tregs) expressing proteins like FoxP3, CD25, GITR, and the CCR4 receptor (Charles-RM-Bangham et al., 2015). Tregs not infected by HTLV-1 might hinder the effectiveness of the CTL response to HTLV-1, thus elevating the proviral load and disease risk (Charles-RM-Bangham et al., 2015). Primary ATL cells often express Treg proteins, as do some non-malignant HTLV-1-infected cells (Charles-RM-Bangham et al., 2015). However, in HTLV-1-infected Tregs, Tax and HBZ genes impair FoxP3 expression and function, rendering HTLV-1-infected FoxP3+ cells ineffective at regulation (Charles-RM-Bangham et al., 2015). Therefore, while ATL may originate from a Treg clone, it's not necessarily a malignancy of Tregs

(Charles-RM-Bangham et al., 2015). However, since Tax is a transactivator it is able to activate many oncogenic pathways by activating the HTLV-1 LTR promoter which allows for the transcription of the virus (Inbal-Arzan et al., 2004). Tax transactivates through Tax responsive elements, which are 3 imperfectly conserved repeats (Inbal-Arzan et al., 2004). It contains a sequence homologous to a matching cAMP sequence (Inbal-Arzan et al., 2004). This triggers a signaling pathway which activates HTLV-1 gene expression (Inbal-Arzan et al., 2004). Additionally, Tax alters telomeres and topoisomerase I expression (Inbal-Arzan et al., 2004). Telomeres preserve DNA and are located at the ends of DNA strands (Inbal-Arzan et al., 2004). HTLV degrades the telomeres; without protection the DNA will eventually reach a point where it is to short and become ineffective and cause a cell to undergo apoptosis or cause severe chromosome mutations such as aneuploidy, inactive cell checkpoints, translocations, and rearrangements (Inbal-Arzan et al., 2004). These mutations can lead to cancer (Inbal-Arzan et al., 2004). ATL cells, specifically, tend to have more telomere mutations than other cancerous cells, supporting the idea that Tax mutations can give rise to ATL (Aurore-Sommer 2020). Topoisomerase is involved in DNA repair and the cell cycle (Inbal-Arzan et al., 2004). Tax mutates it so that cell apoptosis stops and therefore there is an uncontrollable amount of cell division and mutated cells, providing a higher risk for cancer (Inbal-Arzan et al., 2004). Although there is a small amount of Tax in a HTLV population, it is necessary for the cell to replicate and spread, making it an essential protein in HTLV-1's leukemogenesis (Inbal-Arzan et al., 2004).

Rex Gene
Rex is an important regulatory gene which binds to the Rex Responsive Element and post transcriptionally regulates mRNA (Kazumi-Nakano et al., 2012). It exports any HTLV-1 mRNA from the nucleus and into the cytoplasm (Nakano & Watanabe, 2012) . When the double spliced mRNA of accessory proteins is transcribed, Tax activates 5' LTR for enhanced transcription (Nakano & Watanabe, 2012). However, P30[II] binds to double stranded tax or rex and remains in the nucleus, effectively suppressing rex function; More Rex will bind to P30[II] in order to switch back onto a replication period (Nakano & Watanabe, 2012). This works to the virus's advantage; it allows the virus to cycle between periods of high replication and periods of latency (low to no replication) (Nakano & Watanabe, 2012). Rex forms 4 stem loops which assist the virus with polyAsingle and polyA binding sites (Nakano & Watanabe, 2012). Rex can also lead to increased RNA function in unspliced transcripts when Cis Acting Repressive sequences suppress R activity. 5' Cis acting Repressive sequences are found only in unspliced mRNA while 3' is conserved (Nakano & Watanabe, 2012). Then, CRM1 selectively transports Rex out of the nucleus, allowing for translation of the virus's structural proteins for replication to occur and for cytoplasmic accumulation (Nakano & Watanabe, 2012). Additionally, Rex is important for a cell's homeostasis. Utilizing phosphorylation, Rex is able to interact with many proteins. For example, Rex upregulates il-2ra, a type of mRNA which is an adverse prognostic factor for ATL (Nakano & Watanabe, 2012). Rex controls the expression of many transcripts (Nakano & Watanabe, 2022). It has been found that Rex may be able to choose splicing preference meaning it can cause dysregulation of splicing in HTLV cells and change the ratio of oncogenes within cells (Nakano & Watanabe, 2022). Tax is responsible for the activation of the Serum Response Factor, which has control over many genes (Nakano & Watanabe, 2022). Additionally, it controls the Serum Response Factors transcription, effectively controlling the Serum Response Element. The Serum Response Element has control over many growth regulatory genes; when Rex mutates it, there will be havoc in the cell cycle which can potentially lead to

cancer (Nakano & Watanabe, 2022). Furthermore, Rex also can cause mutations in cell cycle checkpoints due to its interactions with cDKs (Nakano & Watanabe, 2022). Without checkpoints and an uncontrollable cell cycle, there is a very high chance cancer, specifically ATL as CD4+ cells are infected, will form (Nakano & Watanabe, 2022). Overall, Rex is most common in early infection but enhances cancer risks throughout the virus's infection.

HBZ Overview

HBZ or HTLV-1bZIP factor encodes many viral genes and is the most important factor of Leukemogenesis from HTLV-. The bZIP factor binds CREB2 to HTLV-1, triggering the amplification, resulting in unspliced (usHBZ) and spliced HBZ (sHBZ)(Zhao, 2016). Both transcripts do not contain a TATA promoter. sHBZ's transcription is activated by Tax Responsive Elements and protein Sp1 (Matsuoka & Green, 2009). However, Tax induced antisense transcription isn't very common as there are often low levels of Tax in most infected cells (Matsuoka & Green, 2009). While both transcripts have very similar sequences, both have different functions. usHBZ can only be activated using Tax, making it less common than sHBZ (Matsuoka & Green, 2009). Studies have shown there is around 4x more sHBZ than usHBZ in all ATL patients and HTLV-1 infected individuals (Zhao, 2016). Only T-cells with sHBZ have growth promoting activity (Zhao, 2016). UsHBZ can suppress transcription by interacting with transcription factor c-Jun and transporting it into the proteasome (Ahmadi Ghezeldasht et al., 2013). The differences between the two stem from a difference in the first exon which relates to the Rex Responsive Element, signaling the differences in transportation abilities between the two (Ahmadi Ghezeldasht et al., 2013).

Tax and HBZ

Tax and HBZ are directly related in leukemogenesis of ATL. As mentioned before, Tax is often mutated or deleted during the virus's life cycle (Aurore-Sommer 2020). Therefore it is present in only about 60% of ATL cases while HBZ is always expressed (Zhao, 2016). This may be because HBZ has a much lower immunogenicity than Tax, allowing the virus to survive for longer (Ahmadi Ghezeldasht et al., 2013). Additionally, CTLs target Tax, causing major loss of its expression (Ahmadi Ghezeldasht et al., 2013). Furthermore, Tax and its binding sites are mainly located at 5', this area is subject to hypermethylation, silencing the area and signaling that Tax isn't vital for the formation of ATL (Mahgoub et al., 2018). However, HBZ and Sp1 binding sites are located on 3', a highly conserved area (Mahgoub et al., 2018). Paired with the fact that HBZ and proviral load are correlated, it is apparent that HBZ is the most important factor of ATL occurring. Tax and HBZ work together to control the virus's replication (Mahgoub et al., 2018). Tax activates nuclear factor NF-kB, which can alter T-cells (Mahgoub et al., 2018). While this alteration can be cancerous, it can cause the cell to become weak due to its defense mechanisms (Mahgoub et al., 2018). Therefore, HBZ down regulates this process with p65 degradation, allowing the cell to go into a latency period and persist (Mahgoub et al., 2018). In general, Tax is necessary for HTLV-1 to proliferate but not necessary for the formation of ATL, despite the fact that it is oncogenic.

HBZ and ATL

HBZ can cause cancer due to many reasons. It promotes the expansion of regulatory T cells (Treggs) by suppressing CD4+ T cells (Zhao, 2016) . This weakens the cell's immunity and

allows for further infection of HTLV-1(Zhao, 2016). This leads to uncontrollable cell proliferation, which will eventually cause cancer, specifically ATL (Zhao, 2016). Furthermore, HBZ causes genetic instability through mutation in infected cells which promotes leukemogenesis and tumor maintenance (Zhao, 2016).

Prognosis and Pathophysiology of ATL

Overall, ATL-affected individuals have a poor prognosis (Durer & Babiker, n.d.). This is because this specific cancer is chemoresistant, making treatment options difficult to find (Durer & Babiker, n.d.). There are 4 subtypes to this disease: acute, lymphoma, chronic, and smoldering (Durer & Babiker, n.d.). Acute ATL results in an abnormal amount of leukocytes in the blood and lymphatic system (Durer & Babiker, n.d.). Lymphoma ATL causes abnormal amounts of leukocytes in the blood only (Durer & Babiker, n.d.). Chronic ATL develops slowly and affects the lymph nodes and blood (Durer & Babiker, n.d.). Smoldering ATL is considered low grade as it can go on for long periods of time without causing many issues but primarily affects the skin and lungs (Durer & Babiker, n.d.). As stated previously, ATL is caused by HTLV-1. This retrovirus's genes promote infection of T-cells, causing uncontrolled cell division (formation of tumors), in the blood and lymphatic system (Zhao, 2016). Specifically, CD4+ T-cells are infected and transformed, causing cellular proliferation; HTLV-1's Tax gene gives rise to tumor maintenance but HBZ allows for tumor maintenance (Zhao, 2016).

Overall, HTLV-1 is a complicated retrovirus with many links to ATL. The genes: tax, rex, and HBZ are seen to be directly correlated with this leukemogenesis. Specifically, HBZ can be seen as the most important factor in the progression of a simple infection into cancer. There are various biological methods for ATL to form from these important genes.

Treatment of HTLV-1

There isn't a specific cure for this virus yet, but there are many experimental procedures in place.

1) Vaccine

In the modern day, there are many vaccines to protect us from a multitude of illnesses. Specifically, there is already a magnitude of antiviral and anticancer vaccines. HTLV-1 is very common in some areas, with infection rates up to 50% (Eusebio-Ponce et al., 2019). In areas like this, a vaccine would help tremendously as to aid fighting the virus and its complications. A vaccine involving HTLV-1's envelope glycoprotein could be efficient because the glycoprotein has a key role in initiating viral pathogenesis because it holds the virus to the receptor (Ratner, 2022). Additionally, studies show there are immunogenic epitopes in the glycoprotein which can cause a human response (Ratner, 2022). However glycoproteins are very sensitive to mutation's which leave them dysfunctional, resulting in a noneffective vaccine (Ratner, 2022). Therefore vaccines involving the Tax gene are most favored (Ratner, 2022). Tax is extremely stable as it is a part of HTLV-1's genetic makeup and directly involved in cellular proliferation and formation of

tumors (Ratner, 2022). A vaccine with Tax would attempt to reduce the cellular proliferation and the proviral load by improving the virus's CTL response (Ratner, 2022). High CTL response means lower proviral load, resulting in a lower chance of developing ATL (Ratner, 2022). In a vaccine for BLV(Bovine Leukemia Virus) altering the Tax expression of the BLV resulted in the virus being able to replicate with very low efficiency (Ratner, 2022). This vaccine is available commercially (Ratner, 2022). HTLV-1 and BLV are quite similar so it is entirely plausible to apply the same principles (Ratner, 2022). BLV is also a retrovirus which causes a form of leukemia containing Tax and Rex, exactly like ATL (Ratner, 2022). Unfortunately, there hasn't been enough research nor information known about a vaccine or the HTLV-1 infection available for a specific vaccine or theory (Ratner, 2022).

2. Antiretroviral Therapy (ART):

Combining AZT (Zidovudine) with interferon alpha (IFNa) has shown efficacy in treating Adult T-cell Leukemia (ATL) (Bazarbachi & Hermine, 1996). IFNa suppresses Tax expression through upregulation of PKR (Bazarbachi & Hermine, 1996). Tax has a large role in leukemogenesis, and if suppressed could stop the formation of malignancies (Bazarbachi & Hermine, 1996) . AZT has an unclear role but may be linked to cell apoptosis (Bazarbachi & Hermine, 1996). Despite its lack of clarity, AZT + INFa is much more efficient than either one alone (Bazarbachi & Hermine, 1996). Overall, both work together to suppress viral replication. However, there is a lack of information on ideal treatment time and biomarkers, meaning this potential cure has to be researched more.

Furthermore, studies have found that combining arsenic trioxide with a low dose of AZT + IFNa has an even larger effect on disease control specifically in patients with chronic type ATL (Kchour et al., 2013). This study has only been done on a small number of patients and needs further experimenting (Kchour et al., 2013).

3. Integrase Strand Transfer Inhibitors (INSTIs):

There are limited studies that explore the use of INSTIs in treating HTLV-1 infection and ATL. Integrase inhibitors diketo acids and styrylquinolines inhibit strand transfer reactions by inhibiting the number of integration events (Marino-Merlo et al., 2020). They can also variably inherit the proviral load spread by PBMCs (Marino-Merlo et al., 2020).

Additionally, integrase inhibitors Raltegravir and isentress inhibited HTLV-1 integrase in vitro which can lead to decreased proviral load (Marino-Merlo et al., 2020). Monotherapy with Raltegravir was shown in a study to be only a transient inhibitor for around 6 months, meaning it only temporarily suppressed the ATL for 6 months before it stopped (Marino-Merlo et al., 2020).

Similarly, integrase inhibitor bictegravir was approved by the FDA as it is more effective than Raltegravir + Isentress (Marino-Merlo et al., 2020). While it showed greater inhibition in cell-free assays, bictegravir is around 20 times less efficient in inhibiting integration than infection in vitro; possibly because of the high efficiency the drug would need to enter the target cells (Marino-Merlo et al., 2020). As there is a lack of studies there are questions of the efficiency of

this drug in vivo (Marino-Merlo et al., 2020). This inhibitor also seems to only have transient effects (Marino-Merlo et al., 2020).

The effectiveness of INSTIs in inhibiting proviral load in patients remains unclear.

3. Protease Inhibitors:

The Protease inhibitor Ritonavir shows potential effects in inhibiting HTLV-1. Ritonavir inhibits NF-kB activation in Tax-transfected lymphoid cell lines, regulating apoptotic genes (Marino-Merlo et al., 2020). It has demonstrated antitumoral effects in an ATL animal model, reducing lymphocyte infiltration and organ enlargement (Marino-Merlo et al., 2020). Ritonavir possibly targets cellular determinants induced by HTLV-1 infection, allowing HTLV-1's inhibition (Marino-Merlo et al., 2020). However there are limited studies, which show evidence of potential benefits in inhibiting HTLV-1-related complications (Marino-Merlo et al., 2020).

4.Mogamulizumab:

Mogamulizumab is a monoclonal antibody which targets the CCR-4 receptor, causing a reduction in HTLV-1 infected cells (Sato et al., 2018). There is a high response rate and it demonstrates a great response, especially in acute-type ATL (Sato et al., 2018) . Studies which combine Mogamulizumab with other treatments, such as Allo-HSCT and VCAP-AMP-VECP, show varying complete response rates (Sato et al., 2018). Some challenges are the increased risk of severe graft-versus-host disease (GVHD) and potential limitations in treating lymphoma-type ATL (Sato et al., 2018). Mogamulizumab's effectiveness may vary depending on the combination regimen used (Sato et al., 2018).

Name of Drug	Mechanism	Strength	Limitations
Vaccine	Targets Tax gene to improve cellular immune response, reducing cellular proliferation and proviral load	Potential long term solution to decrease HTLV-1 transmission and effects such as ATL	Challenges with glycoprotein mutations, which may render vaccine ineffective
AZT	Inhibits reverse transcriptase, thereby suppressing viral replication.	Demonstrated efficacy in reducing proviral load and prolonging survival in patients	Lack of clarity on its role in ART. Efficacy in combination therapy with IFNa, its specific mechanism and contribution to treatment

		with ATL.	outcomes does not have enough research.
IFNa	Suppresses Tax expression through upregulation of PKR, inhibiting viral replication and potentially halting leukemogenesis.	Effective in combination with AZT, leading to significant responses and improved clinical outcomes in ATL patients.	Limited information on ideal treatment time and biomarkers. Lack of information on optimal treatment protocols, necessitating further research.
Arsenic Trioxide	Enhances disease control when combined with AZT + IFNa, particularly in chronic-type ATL.	Shows promise in improving treatment outcomes in patients with ATL	Limited data on efficacy and safety: Studies are limited and require further experimentation to establish its effectiveness and safety.
Integrase Inhibitors	Inhibit HTLV-1 integrase, leading to decreased proviral load and potentially controlling viral infection.	Potential for reducing proviral load in vitro, indicating a possible benefit in treating HTLV-1 infection.	Limited studies and data, leading to uncertainties about their effectiveness in vivo.
Protease Inhibitors	Ritonavir inhibits NF-kB activation in Tax-transfected cell lines, potentially targeting cellular determinants induced by HTLV-1 infection and inhibiting viral replication.	Demonstrates potential antitumoral effects and inhibition of HTLV-1-related complications in animal models	Limited evidence which evaluates the efficacy and safety of protease inhibitors in treating HTLV-1-related complication,
Mogamulizumab	Targets the CCR-4 receptor, causing a	Demonstrates a 100% response rate and	Risk of adverse effects: Mogamulizumab may increase the risk of

	reduction in HTLV-1 infected cells, leading to high response rates, especially in acute-type ATLL.	significant efficacy in reducing HTLV-1 infected cells.	severe graft-versus-host disease (GVHD) and its effectiveness may vary depending on the combination regimen used

Table 1 shows the mechanisms, strengths, and limitations of the discussed treatment options.

Discussion

Overall, this analysis clearly shows there is a lack of research on treatment options of HTLV-1 to assess the best one. All of these treatments are in a relatively early stage and lack valuable information. This highlights the need for further research. However, out of all of these options, Antiretroviral therapy seems the most promising, if given more testing. Studies have demonstrated the efficacy of ART, particularly in combination therapy such as AZT (Zidovudine) with interferon alpha (IFNa). This has shown significant responses, including complete remission and prolonged survival in some patients. The suppression of Tax expression by IFNa and the inhibition of viral replication by AZT contribute to the overall effectiveness of this regimen. Compared to classical chemotherapy, ART has been associated with better clinical responses, especially in chronic-type ATL. Patients undergoing ART have shown higher rates of survival, with a median survival time of 18 months. This indicates that ART not only controls the disease but also extends the lifespan of patients, improving their quality of life. Additionally, ART allows for combination therapy, enhancing its effectiveness. The combination of ART with other agents such as arsenic trioxide, which has shown even better disease control, particularly in chronic-type ATL. This demonstrates the versatility of ART in being integrated into multifaceted treatment approaches, and highlighting the promise of this medication.

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