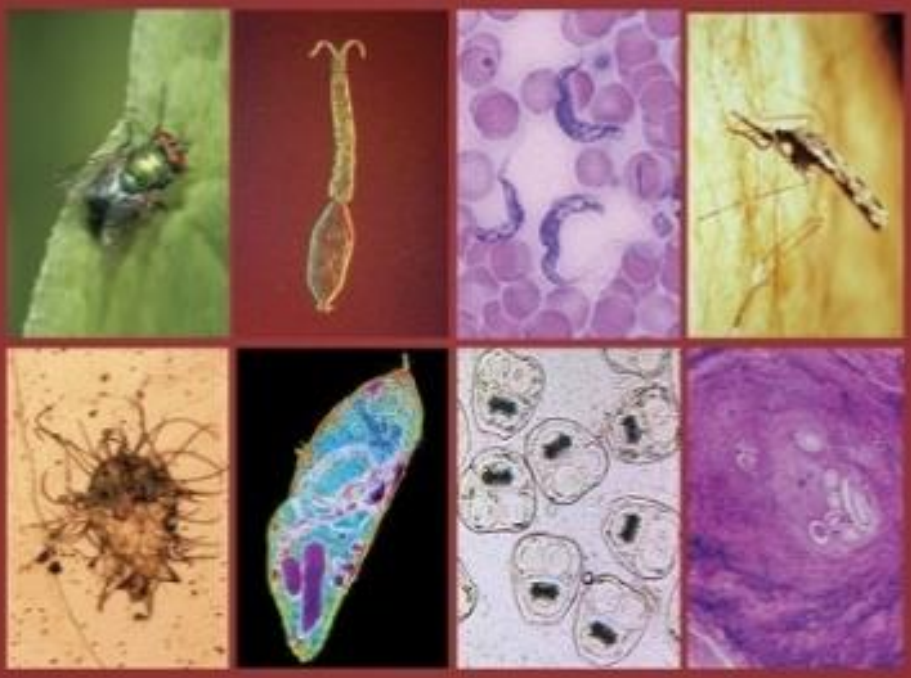
EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

E

MEDICAL ENTOMOLOGY & PARASITOLOGY



ISSN
2090-0783

WWW.EAJBS.EG.NET

Vol. 15 No. 1 (2023)

Citation: *Egypt. Acad. J. Biolog. Sci. (E-Medical Entom. & Parasitology Vol.15(1) pp **21-44**(2023)*
DOI: 10.21608/EAJBSE.2023.292468

Egypt. Acad. J. Biology. Sci., 15 (1):21–44 (2023)

Egyptian Academic Journal of Biological Sciences
E. Medical Entomology & Parasitology

ISSN: 2090–0783
www.eajbse.journals.ekb.eg

Parasitism and Molecular Implication of HTLV-1 Pathogenesis

Almalki, Shaia S.R.
Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University
***E-mail:** almalkishaia@hotmail.com

REVIEW INFO
Review History
Received:13/2/2023
Accepted:28/3/2023
Available:6/4/2023

Keywords:
HTLV-1-transmission; HBZ, tax; viral oncogenesis; ATLL; TSP/HAM; treatment;

ABSTRACT

Human T-cell Leukemia disease type 1 (HTLV-1) is a retrovirus of oncogenic nature that is competent at its role to cause life-threatening diseases in the human population, for instance, a powerful lethal condition termed Adult T-cell Leukemia/Lymphoma (ATLL) and more occasionally neurological condition termed as Tropical Spastic Paraparesis (TSP) which is also termed as HTLV-associated Myelopathy (HAM). Experts give an estimation of ten-twenty million persons impacted by HTLV-1 intercontinental. The epidemiology that is poorly understood, the unavailability of vaccines and the absence of targeted anti-retroviral treatment have compelled the Global virus network to dispatch a task group in the year 2014. They focussed mainly on the enhancement of various possible procedures for the clinical management (examination and treatment) of the people infected with HTLV-1. HTLV-1 Transmission at a cellular level is achieved via contact of one cell with another and generation of plenty of infected cesses so that it can hang on there and accomplish transmission of infection to another vulnerable host. Viral propagation through cell-to-cell contacts leads to the enhancement of a load of the provirus. The enhanced load of the provirus is a significant factor allied with the progression of ATLL and other inflammation-associated diseases. The tax and HTLV-1 bZIP factor (HBZ) are the virally encoded genes that through their accommodating actions accomplish variation of the immunophenotype of infected cells, induction of proliferation and apoptotic inhibition of the cells to enhance the number of infected cells. Subsequently, infected cells hang tight, multiply and infiltrate into the tissues, which is probably the key factor for the transmission of HTLV-1. Both kinds of HBZ (protein and mRNA) play a crucial role in the oncogenesis of HTLV-1. The structural configuration of HBZ protein (shape) with its relationship with host cell proteins, for instance, p300-CBP, Foxo3a as well as Foxp3 execute different key roles (apoptotic process, proliferation augmentation, and anti-viral activity weakening) so as to modify transcription profile of T-cells and thus provoking the development of oncogenesis. The current article is basically occupied with determining the initiation of HTLV-1 infection, the strategy of cellular transmission, disease development at a molecular level and related prophylaxis and treatment.

INTRODUCTION

It is evaluated that around 20% of the aggregate instances of malignancy are caused by viral disease (Bouvard *et al.,* 2009). Distinguishing proof of HTLV-1 infection was completed well before around 40 years by Robert Gallo's group in 1980 in the US (United States) and Japan (Poiesz *et al.,* 1980; Yoshida *et al.,* 1982), even preceding the revelation of Human Immunodeficiency Virus (HIV-1)(Barré-Sinoussi *et al.,* 1983).

An estimation of around 10 million individuals is infected with HTLV-1 intercontinental (Gazon *et al.,* 2012). The major endemic region for HTLV-1 infection in South America (SA), Africa (sub-Saharan) and Japan while a few cases of infection have been recorded in the Middle East and Australo-Melanesians (also Australasian, Australomelanesoid or Australoid) regions(Gessain and Cassar 2012). HIV-1 and HTLV-1 both are retroviruses having a similar source of development in the human population from the simian population by means of zoonotic transmission (Interspecies transmission from monkeys(Keele *et al.,* 2006; Vandamme *et al.,* 1998). It has simian inception named as simian T-cell leukaemia Virus type 1 (STLV-1). Following its discovery, description and depiction it was seen that an oncogenic HTLV-1 was a causative factor of both a rapidly progressive harmful lymphoproliferative condition termed as Adult T-cell Leukemia/Lymphoma (ATLL) and sporadically lethal neurological condition termed as HTLV-1-associated Myelopathy which is also named as Tropical Spastic Paraparesis (Gallo 2005; Gessain *et al.,* 1985; Hinuma *et al.,* 1981). Various sicknesses and disorders, for example, uveitis, conjunctivitis, interstitial keratitis, infective dermatitis, myositis, joint pain, respiratory ailments, Sjogren's syndrome, sicca disorder, Graves' illness, Hashimoto's thyroiditis, and polyneuropathies have been seen in both carrier and patients of TSP/HAM or ATLL(Gonçalves *et al.,* 2010; Kamoi and Mochizuki 2012). Crusted scabies, Strongyloides stercoralis, tuberculosis and leprosy have also been seen as an opportunistic infection in patients experiencing ATLL(McKendall 2014). 2 - 4% of HTLV-1-infected people have been found to build up an ATLL while 1 - 2% a TSP/HAM condition. The three main routes are the vertical transmission from the mother's breast to a child due to extensive stretch of breasting(Hino 2011), unprotected sex (Kaplan *et al.,* 1996) and infected blood products (Figure 2a). Transmission of HTLV-1 provirus at the cellular level happens by means of cell-to-cell communication(Igakura *et al.,* 2003; Pais-Correia *et al.,* 2010), whereas freely moving virions show lower infectivity except for their tissue tropism towards dendritic cells (DCs) which may get infected with no contribution of the cell-to-cell communication system(Alais *et al.,* 2015; Derse *et al.,* 2001; Jones *et al.,* 2008; Mazurov *et al.,* 2010). It contrasts from HIV-1 retrovirus as it increases and elevates in its count fundamentally by proliferating infected cells which leads to the successful transmission of the virus(Cavrois *et al.,* 1998). Only very limited diagnostic methodologies apart from serological screening are existing and a slight effort has been pushed forward for identification of infected individuals and for reduction in transmission of the disease. No any vaccines or targeted effective treatment choice at present exists for complete remission of the disease. Remembering the given circumstance, the Global Virus Network (GVN) propelled a team in 2014 to energize elementary research, improvement of methodologies of counteractive action and discover the successful treatment of HTLV-1 disease so that new general public health measures can be prescribed and recommended. This article presents strategies for transmission at fundamental to cell level, portrayal of HTLV-1 related sicknesses, sub-molecular system of pathogenesis, oncogenesis (Leukemogenesis), immunological aspects, ways to deal with prophylactic vaccine development and current therapeutic choices together with future perspective of immunization and therapeutic development.

Genomic Association of HTLV-1 Proviral Genome and The Key Elements of The Gene Products:

HTLV-1 is a perplexing retrovirus with leukemogenic nature having

an ssRNA (+) genome encoding for special proteins that has oncogenic potentiality. It is an enveloped virus and the inner membrane of the envelope is mainly lined by matrix protein which encases the capsid of the virus. The viral capsid contains genomic RNA (two indistinguishable strands) and catalysts (useful protease, integrase and turn-around transcriptase). A naturally created viral molecule sticks to the receptor of the host or target cell with the assistance of an envelope and enters the cell by combination process by uncovering capsid substance in the cytoplasm of the cells targeted. Viral genomic RNA produces DNA (twofold stranded) by the process of reverse transcription which is transported to the core and its reconciliation with the host chromosome gives rise to what is actually known as the provirus. The definite hereditary HTLV-1 provirus structure as well as the key elements have been clarified in Figure 1. In spite of the fact that it is fundamentally like other complex retroviruses, it has gag, env and pol (structural genes), rex and tax as administrative genes and other adornment genes (HBZ, p13, p30 and p12,(Matsuoka and Jeang 2007). Provirus has enhancer and promotor components for the commencement of translation into the long terminal repeats (LTR) and the polyadenylation signal for positive strand transcription is arranged in 3′LTR(Poiesz et al., 1980). It codes for the structural proteins, polymerase and envelope from un-spliced or singly spliced mRNAs(Lee *et al.,* 1984; Nam *et al.,* 1988; Paine *et al.,* 1994). ORF (Open Reading Frames) IV and III encode tax and rex respectively sharing a common doubly spliced transcript. Transactivator gene (tax) is in charge of improving the rate of LTR-interceded viral translation(Cann *et al.,* 1985; Felber *et al.,* 1985; Inoue *et al.,* 1987) and modulating the transcription of different genes especially associated with the procedure of cell multiplication, cell differentiation, cell cycle control and DNA repair(Kashanchi and Brady 2005; Leung and Nabel 1988; Mulloy *et al.,* 1998). The oncogenic capability of tax (Grassmann *et al.,* 1992; Yamaoka *et al.,* 1992) and its huge job in human T cells transformation by HTLV-1 and 2 have been previously noted(Robek and Ratner 1999; Ross *et al.,* 2000). Immunogenicity of the tax protein is high when contrasted with that of HBZ proteins(Hilburn *et al.,* 2011; Jacobson *et al.,* 1990) and that is the reason why a cell infected with HTLV-1 can express HBZ under immunological surveillance of the host while the expression of tax is too much restricted. On the other hand, the Post-transcriptional activity of rex is to attach, stabilize and send out intron-containing mRNAs to the cytoplasm of the target cell from the nucleus(Younis and Green 2005). The study has shown that Open Reading Frame -1 (ORF I) and Open reading frame-2 (ORF II) codes for p12/p8 and p30/p13 respectively are vital for infection initiation and to establish the persistence in the animal model and cell culture(Collins *et al.,* 1998; Valeri *et al.,* 2010). Accessory proteins, for example, p8 (protiolytically cleaved result of p12) and p13 polypeptide (contained the carboxy end of p30) may likewise assume a crucial role in causing quiescent T cells in vitro infection(Albrecht *et al.,* 2000; Nicot *et al.,* 2005; Younis *et al.,* 2004). HBZ gene (encoded on – strand of the provirus) is transcribed from 3' LTR, though rest of the viral genes are transcribed (as sense transcript) via the 5' LTR, That can be widely induced by tax encompassing p300/CBP(Nyborg *et al.,* 2010), in vitro and while in vivo, discontinuous transcription of tax and consistent expression of HBZ including SPI basically has been noted (Yoshida *et al.,* 2008). Modulation of both the cell and viral gene translation is coordinated by basic cooperation of HBZ with different cell factors, for example, JunB, JunD, c-Jun, CREB restricting protein (CBP)/p300 and cAMP(Basbous *et al.,* 2003; Clerc *et al.,* 2008; Gazon et al., 2012; Thebault *et al.,* 2004). HBZ plays a huge role in T-cell multiplication (Arnold *et al.,* 2008; Satou *et al.,* 2006). Tax as the

viral oncoprotein has been confirmed in the greater part of the study however recently developing information giving the idea of supporting job of HBZ in the process of oncogenesis. It gives the idea that the tax and HBZ genes (encoded individually on + and – strand of provirus) are controlled reciprocally which is confirmed in infected cells treated with valproate, where there was higher tax expression, the transcript of HBZ was supressed(Belrose *et al.*, 2011). Assembly and maturation of virion, entry of virus and transformation tropism, viral persistence, the infectivity of the virus and persistence, positive posttranscriptional regulation and, oncogenesis and viral transcription are accomplished by gag and pol, env, p13, p12, rex and tax genes respectively.

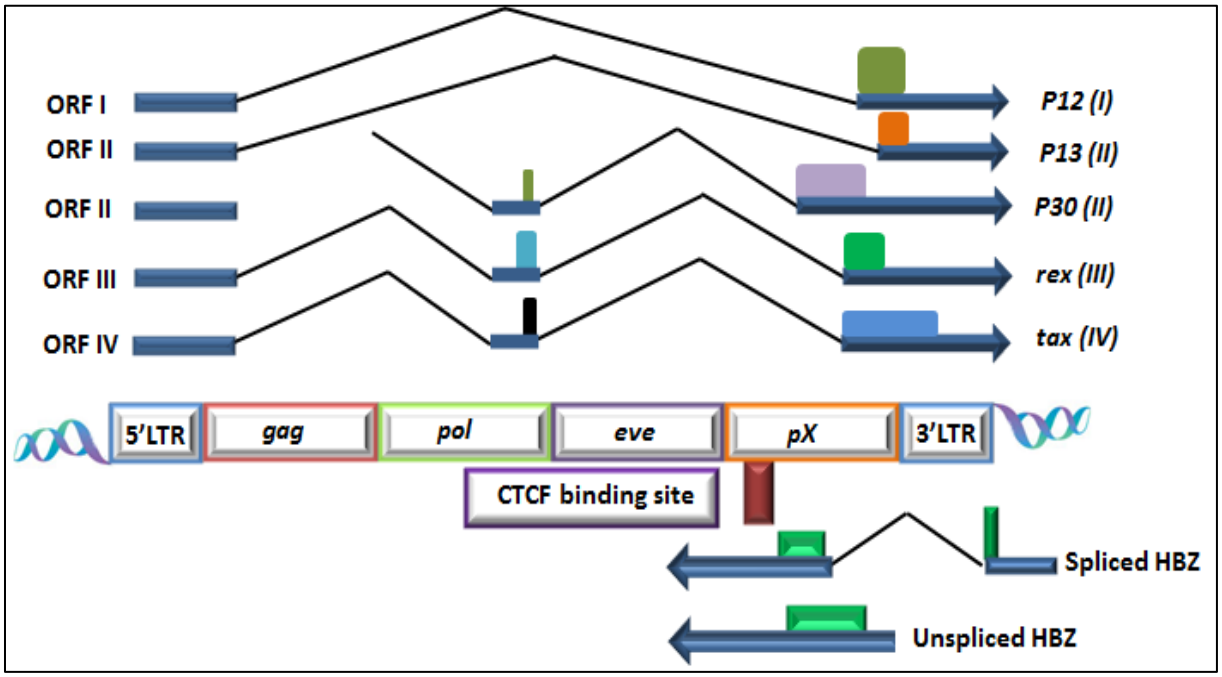


Fig. 1: HTLV-1 provirus genomic composition with details of all the potential genes. The restriction site CTCF has been depicted as a red bar in HBZ coding area**.**

Transmission of HTLV-1: Routes of Transmission and Preventive Measures:

The three main routes are the vertical transmission from the mother to the young ones due to prolong breastfeeding (Hino 2011), unprotected sex(Kaplan e*t al.*, 1996) and infected blood products (Fig. 2a). The mechanism of infection to cells from the former cells with infection to the new cells of the host is unclear though it leftovers an open investigation that whether breast conduit epithelia add to the viral transmission through milk(Martin *et al.*, 2012; Southern and Southern 1998). HTLV-1 virions have low infectivity with effectiveness to transmit by means of cell-to-cell infections (Mazurov *et al.*, 2010) as the infected cells (from a virological synapse) (Igakura *et al.*, 2003) allow viral particles to transfer to uninfected cell efficiently which leads to the de-novo infection(Igakura *et al.*, 2003). Accordingly, the conceivable courses of infections are confined to the accompanying 3 modalities in which the transfer of living infected cells is fundamental, which have been portrayed in Figure 2a. The provirus is predominantly seen in effector or memory CD4+ cells which proposes that this sub-population gets infection with HTLV-1(Yasunaga *et al.*, 2001). The T-lymphocytes present in semen and breast milk are mostly effector or memory T-cells(Bertotto *et al.*, 1990).

````
````

Vertical transmission through breastfeeding is the most dominating route(Wiktor *et al.,* 1993).

Transmission rates (sixteen percent for infants born to mothers carrying the infection, twenty-seven percent for infants nourished by mothers who remained infected for a longer period or more than 90 days of infection and five percent for youngsters who were fed by mothers carrying infection for less than 90 days(Nyambi *et al.,* 1996). As per an estimate, HTLV-1, linked to blood transfusion needs at least ninety thousand virus-infected cells to commence infection processes in the host(Sobata *et al.,* 2015). As the free virion is absent in infected patients (Demontis *et al.,* 2015), the infected cells themselves lead to transmission. It isn't completely contemplated however CD4+ cells or macrophages probably remained critically involved(Pique and Jones 2012). HTLV-1 immunoglobulin screening amid blood transfusion (at first established in Japan in 1986 and pursued by the USA, France, Greece, Portugal, Sweden, UK, and Ireland) has definitely diminished the count of new cases of infection of HTLV-1. The cost viability of the antibody screening measures has been an issue in the zone with lower predominance and therefore numerous other preventive steps or measures should be implemented (Murphy 2016). Pregnant women screening has been executed for HTLV-1 antibody to constrain the transmission through delayed breastfeeding and unprotected sex. The study has supported that Vertical transmission was decreased by ceasing breastfeeding by a seropositive mother(Satake *et al.,* 2016). HIV-1 and HTLV-1 have a similar course of passage (parenteral presentation, unprotected sex and vertical transmission) with a difference in that HIV-1 transmits vertically from the mother to the foetus during pregnancy.

Transmission of HTLV-1 Virus at A Cellular Level:

Proviral HTLV-1 DNA is primarily seen in CD4+ T-lymphocytes (activated)(Richardson *et al.,* 1990). and might be found to a restricted degree in different immune cells, for example, CD8+ T-lymphocyte, B-lymphocytes, dendritic cells and monocytes(Koyanagi *et al.,* 1993; Nagai *et al.,* 2001) (Fig. 2b). Cell-free virions are not particularly infectious with the exception of their tropism towards dendritic cells(Alais et al., 2015; Dutartre *et al.,* 2016; Jones et al., 2008), maybe because of their higher susceptibility than T-lymphocytes to HTLV-1(Alais *et al.,* 2015). The short half-life period (36 minutes at 37 ^{0}C) of HTLV-1 particles is a direct result of its envelopes' affectability to reduction(Shinagawa *et al.,* 2012). Envelopes instability, core particles' intrinsic features and/post entry events contribute to the low infectivity of the HTLV-1 viral particles; actually, the proper transmission of virions necessitates exactly tight contact between a new target cell and an infected cell (Gross and Thoma-Kress 2016). HTLV-1 primary infection is asymptomatic and there is next to no information accessible on the spread rate of the infection particles, particularly amid the proviral load establishment. Its propagation is done in two ways in a nearly similar way to the other exogenous retrovirus (Overbaugh and Bangham 2001). At first re-expression of the proviral genome and formation of enveloped viral particles heads up the infection of a new cell whereas the reverse-transcription of the viral genome is done and ds DNA formed is inserted into the genome of the host that is named as the infection route of replication (Neo-infection). HTLV-1 basically spreads almost wholly by the means of intercellular contact without any release of free virions from infected cells. The three core in vitro mechanisms of cell-to-cell transmission of HTLV-1 have been so far noted and reported as virological synapse(Igakura *et al.,* 2003), virological biofilm(Pais-Correia *et al.,* 2010) and the cellular conduits(Van Prooyen *et al.,* 2010) (Fig. 2c). The

virological neurotransmitter is a specific structure that is named as a compact pocket-like structure separated out between plasma films (a virtual space) in the nearness of the plasma membrane of the uninfected cells where the viral particles bud out and gather for intercellular transfer(Igakura *et al.,* 2003). Intercellular exchange of the HTLV-1 may occur either in the separated out compact pockets between the plasma membrane of the two cells in contact(Majorovits *et al.,* 2008) or on the periphery of the viral neurotransmitter(Pais-Correia *et al.,* 2010). Tax protein plays a key role in the formation of a virological synapse (neural connection) as it co-restricts at the microtubule-organizing centre (MTOC)(Nejmeddine *et al.,* 2005) and up-regulates intercellular adhesion molecule-1 expression (ICAM-1)(Chevalier *et al.,* 2012) whose precise interaction with lymphocyte function-associated antigen-1(LFA-1) situated on an uninfected cell supports the cell-to-cell adherence and additional reorientation of MTOC on the specific site of the inter-cellular contact triggering the polarization of assembly process of the virus(Nejmeddine and Bangham 2010)**.** Extracellular matrix protein (collagen and agrin) and cellular proteins (tetherin and galectin-3) on infected cellular surface grip different particles of the virus producing what is named as viral biofilm which plays a major job in viral transmission more effectively and efficiently as compared to virological neural synapse(Pais-Correia *et al.,* 2010). Biofilm is comparatively more infectious as it might play role in the prevention of recognition by immunoglobulins by masking the epitope of the HTLV-1 virus(Pais-Correia et al., 2010). HTLV-1 regulatory protein p8 expresses to incite generation of cellular conduits (a filopodium-like structure extended towards neighbouring cells) (Sherer *et al.,* 2007; Van Prooyen *et al.,* 2010). At first, LFA-1 clustering at the surface of the cells is induced by p8 regulatory proteins prompting the improved cell-to-cell adhesion by means of interaction ICAC-1 with LFA-1(Van Prooyen *et al.,* 2010). Secondly, HTLV-1 infected cells immortalized by expression of oncoprotein Tax (Matsuoka and Jeang 2007) produce daughter cells (n=2) conveying the provirus on almost the same site of the genome that is named as clonal expansion (Figure 2d), which is considered to be following the neo-infection course of the spread of the virus. 'The clonal expansion' route impose provirus replication by means of DNA Pol2. Provirus integration in the host genome is not executed in a unsystematic way but somewhat it is regulated by four different physical measures(Bangham *et al.,* 2014) such as predominant integration in an open transcriptionally-active chromatin, integration favour within the limit of hundred nucleotides (bound either in a direct fashion by specific proteins like STAT1, TP53 or indirectly by HDAC6 and Brag1) (Melamed *et al.,* 2013), binding of the ubiquitous protein phosphatase 2A (PP2A) with a complex (viral integrase and DNA), inducing of integration site selection(Maertens 2015) and directing of retroviral integration to a key sequence motif of DNA. This DNA motif is generally palindromic but it may sometime be non-palindromic in nature which has been recently stated(Kirk *et al.,* 2016). Both the strands (+ and –) of the host genome carrying this motif nearly in equal numbers, produce a palindromic consensus sequence. Only a single copy or provirus-integrated genome has been detected mostly in naturally infected cell clones(Cook *et al.,* 2017). The infection triggers the expansion or proliferation of the infected cell by expression of genes (HBZ and tax) that results in aggregation of T-cells clone in blood circulation. As a matter of fact, it is the high range of clonal diversity and not oligoclonal proliferation that leads to HTLV-1 inflammation and malignant diseases(Gillet *et al.,* 2011). A couple of cell types get an infection in vivo, for example, dendritic cells,

monocyte/macrophage and epithelial cells, however despite what might be expected the most cell types infected in vitro. Infected macrophages and dendritic cells have been accounted for assume a key job in the start of the HTLV-1 viral propagation and spread (de Castro-Amarante *et al.*, 2015). Dendritic cell is comparatively shows higher susceptibility to infection of HTLV-1(Alais *et al.*, 2015) and are proficient of spreading viruses to the autologous CD4+ cells(Jones et al., 2008) with the help of particular Dendritic cell specific intercellular adherence molecule-3-Grabbing Non-integrin (DC-SIGN)(Jain *et al.*, 2009). The matured dendritic cells are increasingly competent in T-cells infection and transmission process(Rizkallah *et al.*, 2017). CD4+ (about 95% proviral burdens or load) and CD8+ (about 5% proviral burden) cells remain infected with HTLV-1(Melamed *et al.*, 2015). Both the CD8+ and CD4+ T-cells are preferentially infected just in case, they are considered HTLV-1-antigen-specific(Goon *et al.*, 2004). Notwithstanding it, there are so many added factors other than clonality index such as proviral load, amount of the cells with an infection that are undergoing transmission from one person to another and immunological responses are potentially barred in HTLV-1-allied ailments development and progression(Alvarez *et al.*, 2016), which highlights the contribution of both the environmental and genetic factors in disease development. A thought-provoking fact has been stated that the exposure through blood transfusion resulted more possibly to TSP/HAM development of (Osame *et al.*, 1990) whereas by means of breast-feeding resulted in ATLL(Tsukasaki and Tobinai 2012). **I**mmortalized cells clonal expansion finally results in progression of conditions such as ATLL and TSP/HAM (Fig. 2d).

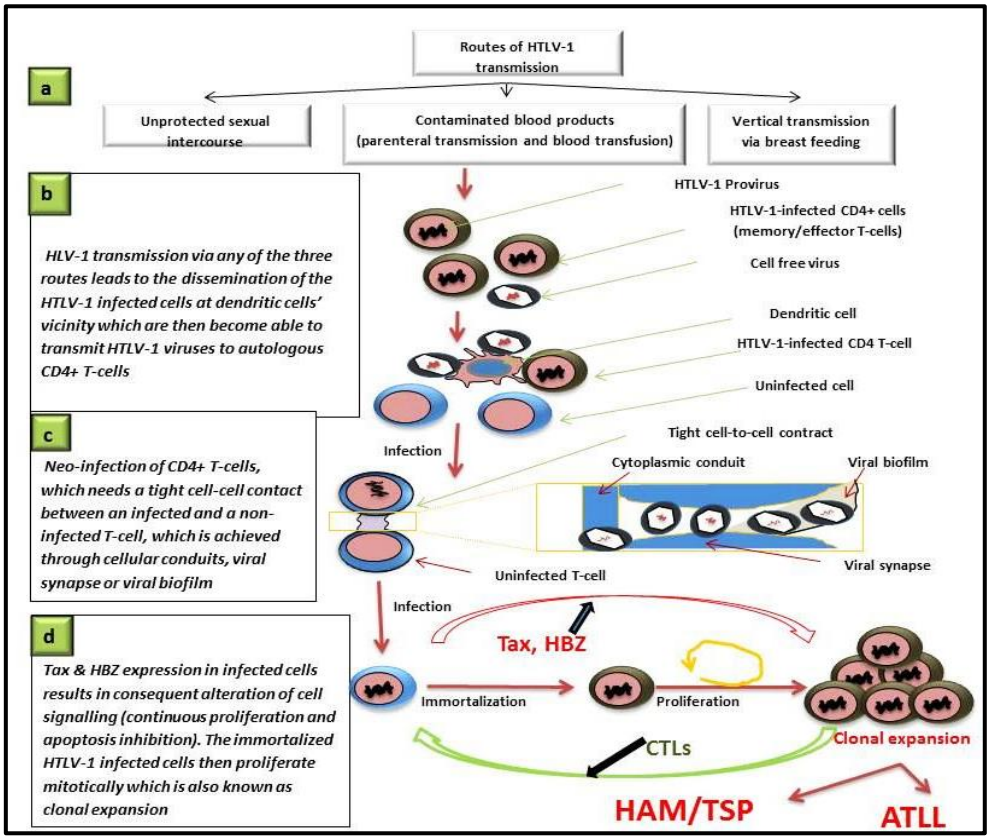


Fig. 2. The course of transmission of HTLV-1 at the section and cell level with the subtleties of the infected cell deification, multiplication and clonal development.

Molecular Mechanism of HTLV-1 Interceded Modification in T-cells for Viral Persistence and Transmission in A Chronic Condition of Infection:

HTLV-1 causes an augment in proviral load following infection essentially by activating the expansion of infected cells through mitotic division. It has been seen that the contribution of de novo infection to the provirus load is not substantially done. Both Tax and HBZ assume a critical job in keeping up the clonal life span and increment in the number of infected cells (cell turnover) which has been portrayed underneath in detail.

Details of Tax Expression and Function:

The size of HTLV-1 provirus is about 9 Kb in length and encompasses genes that encode structural proteins (env, gag and pol), add-on genes (p30, p12, and p13) and regulatory genes for example rex and tax and that are decoded, or transcribed from a positive strand of the proviral DNA whereas HBZ is transcribed as transcripts (antisense). Tax protein unequivocally activates various signalling pathways such as nuclear factor kappa B (NF-kB) as well as Activator protein-1 (AP-1) (Gazon *et al.,* 2018; Grassmann *et al.,* 2005) and in spite of that, tax protein causes in vivo induction of T-cell leukemia or lymphoma (Grossman *et al.,* 1995; Hasegawa *et al.,* 2006). Initiation of NF-kB pathway by tax protein leads to the expression of the cell cycling-related genes CDK2, CDK4, CDK6 cyclin D2, E2F1 and cyclin E(Iwanaga *et al.,* 2001) and anti-apoptotic genes c-FLIP(Okamoto *et al.,* 2006). Cell expansion and cycling are empowered by tax expression through activating PI3 K/Akt pathway (Peloponese and Jeang 2006). In this way, it might be inferred that the outflow of the tax proteins assumes a noteworthy role to hinder apoptosis and supporting cell proliferation. Transcription factors (TCF-1/LEF-1) in the classical Wnt signalling pathway, compromise the tax function (Ma *et al.,* 2015). Nevertheless, curbed expression of TCF-1/LEF-1in effector/memory T-lymphocytes recommends the role of tax protein in these cells, which therefore encourages HTLV-1 to keep up their in-vivo persistence in peripheral effector/memory T-lymphocytes. Tax is the key target antigen that is perceived by CTLs (Kannagi *et al.,* 1991), so its expression is very much arranged and remains normally curbed for the survival of the infected cell from evasion by the host immune response. However all the while, the transient expression of the tax(Mahgoub *et al.,* 2018) assumes a critical role in the maintenance and expansion of the HTLV-1 infected cells.

HBZ Expression and Function:

HBZ is a viral protein encoded by HTLV-1 that has a transcriptionally active domain situated in its N-terminal and leucine zipper motif situated in its terminus C that undertakes a key role in the multiplication of ATL cells and leukemogenesis process (Satou *et al.,* 2006). Maintenance of clonal span is controlled by tax and HBZ expression. Nuclear localization signals remain integrated into its bZIP or main central domain while nuclear export signals are remains incorporated in its N terminus (Hivin *et al.,* 2005). It remains mainly contained in the cytoplasm of blood mononuclear cells in the case of HAM/TSP patients, which is suggestive of its role as a potential biomarker of the disease condition(Baratella *et al.,* 2017). The protein HBZ comprises three domains, for example, central domain (CD), activation domain (AD) as well as basic ZIP domain (bZIP) which upon association with various regulatory protein molecules productively play out the modulation of cellular functions (Figure 4). Interaction of different cellular proteins (transcription factors) at the nuclear level(Basbous et al., 2003; Satou *et al.,* 2011; Tanaka-Nakanishi *et al.,* 2014; Thebault *et al.,* 2004) and at the cytoplasmic level(Kinosada *et al.,* 2017) adds to the hindrance of cell apoptosis and promotion of cell proliferation, which consequently contributes to the disease

````
````

progression (Figure 4). 90% CD4+ effector/memory T cells and 10 % CD8+ T cells have been predominantly observed to be the target cells of the HTLV-1 infection(Yasunaga *et al.,* 2001). HBZ impacts the host T cell differentiation as it influences Foxp3 expression and function (basic controller for the advancing regulatory T cells). The count of T-cells (CD4+Foxp3+) in HBZ-Tg (transgenic) mice has been observed to be enhanced, depictin that expression of Foxp3 is enhanced by HBZ protein(Satou et al., 2011). Initiation of TGF-b/Smad pathway is activated by the up-gradation of the expression of Foxp3(Zhao *et al.,* 2011). HBZ supports Foxp3+ T-cells yet takeovers their transcriptional network prompting the inflammatory disease in the host(Yamamoto-Taguchi *et al.,* 2013). HBZ protein, as well as both of HBZ and RNA, causes up-gradation of the CCR4 expression by initiating the induction expression of GATA3 that heads to the commencement of transcription of a promoter of CCR4 gene. Consequently, it is suggested that HBZ supports the increased T-cell migration and multiplication of infected cells by CCR4 expression enrichment and up-regulation(Sugata *et al.,* 2016). The HBZ protein improves the up-regulation of a co-inhibitory receptor T cell immunoglobulin and ITIM domain (TIGIT) gene(Yasuma *et al.,* 2016) which is generously expressed upon the surface of the cells with infection and ATLL Cells. Significant expression of the TIGIT triggers the generation of IL-10 which eventually represses the immune responses of the host. TIGIT is a co-inhibitory receptor that curbes the activation of T-cell without hindering the proliferation of HTLV-1-infected cells and as well as ATLL cells(Kinosada et al., 2017). Inhibitory signal set forth by TIGIT via intra-cytoplasmic immunoreceptor tyrosine inhibitory motif (ITIM) that lastly interfaces precisely at a molecular level with a complex (THEMIS, SHP-2 and Grb2). Interaction of HBZ to THEMIS results in a hamper of the inhibitory signal from THEMIS which is a T-cell explicit protein proposing that HTLV-1 induces merely T-cells proliferation. HBZ instigates hereditary instability as an infected individual gets capitulated to the ATLL after a long-term latency which is suggestive of apart from tax and HBZ, mounting up of genetic and epigenetic changes which are necessary for the beginning of the ATLL(Grassmann et al., 2005). As of late it has been seen that genomic instability is induced by the HBZ in a miRNA as a way of oncogenic dependency. The protein HBZ augments the expression of miR21 and miR17 (oncomiRs) that suppresses OBFC2A which assists genome stability protection by means of ssDNA binding protein expression, thus causing genomic instability (Vernin *et al.,* 2014). Restraint from apoptosis of these cells carrying infection of HTLV-1 adds to the maintenance of clonal longevity. Foxp3a whose confined localization and function are perturbed by HBZ proteins that down-regulate the Bim and FasL (pro-apoptotic genes)(Tanaka-Nakanishi et al., 2014). Interaction of the N-terminal region of HBZ with IRF-1 leads to the hamper of IRF-1 DNA binding/transcriptional activity which results in a decrease in the number of cells under the process of apoptosis. HBZ RNA also increases promotor activity of surviving for the up-regulated expression of surviving to hinder the apoptosis to maintain the viral persistence and longevity(Panfil *et al.,* 2016).

Interaction of Cellular Proteins in the Cytoplasm and Consequences:

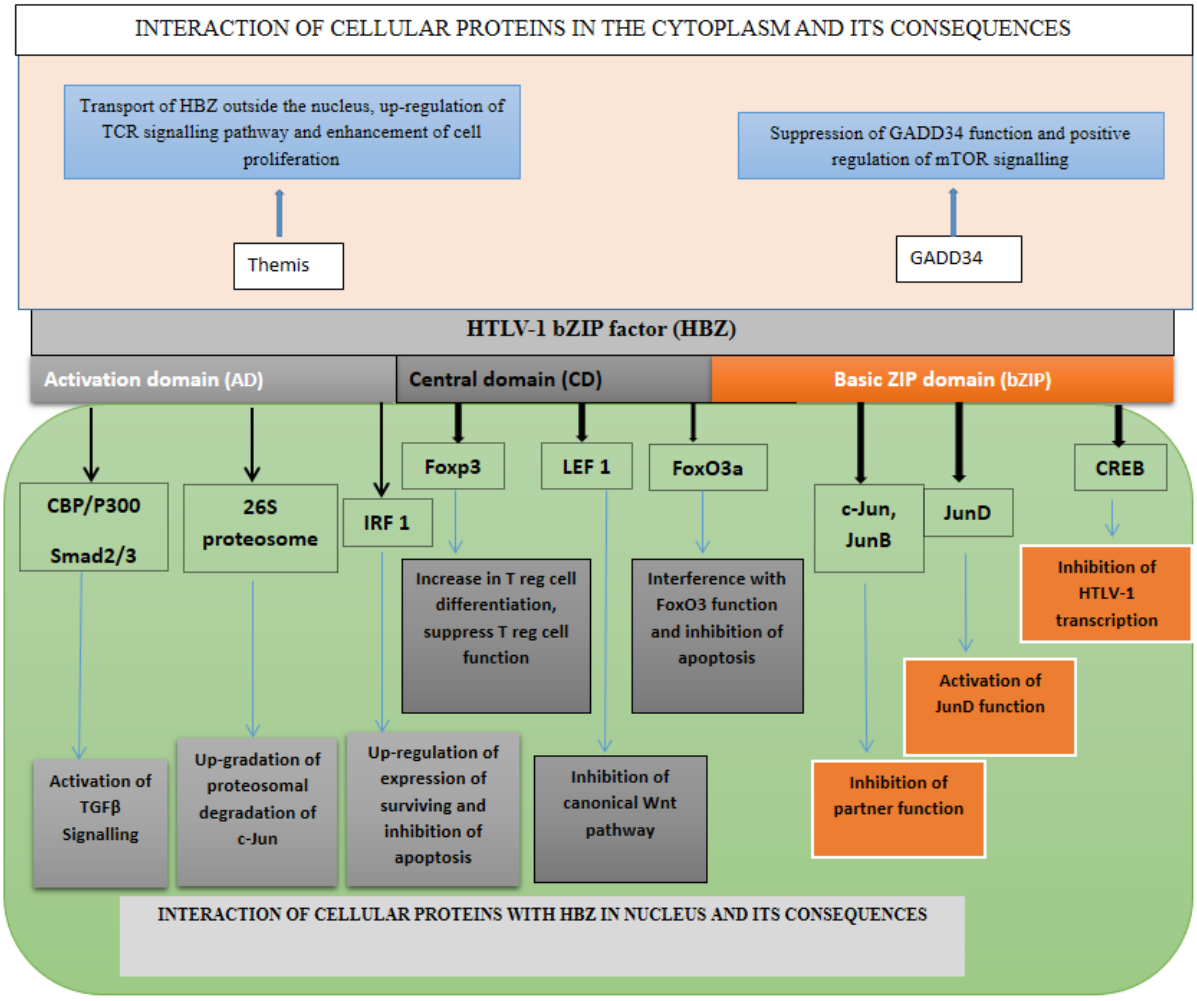


Fig. 4. Depiction of three domains of HBZ as well as the interaction of cellular proteins with HBZ with their consequences in both nucleus and cytoplasm**.**

Adult T cell Leukemia/Lymphoma as a Disease Associated with HTLV-1 and Mechanism of Oncogenesis (leukemogenesis):

ATLL (an extremely aggressive malignant disease of HTLV-1 infected CD4+ cells) develops following a prolonged period of the chronic course of infection (Fig. 2) which was explained earlier before the discovery of HTLV-1 virus while the causal relationship between the HTLAV-1 virus and ATLL was described only a couple of years of discovery of the virus(Yoshida et al., 1982). Clinical highlights, arrangement and biological markers of the ATLL have been well-summarized in Table 1.

````
````

Table 1. Different clinical elements of ATLL with their short portrayal.

Different highlights of ATLL	Brief portrayal	References
Arrangement of ATLL	Four clinical sub-types; chronic, smoldering, intense and lymphoma dependent on diagnostic criteria set down, for example, lymphadenopathy, hepatosplenomegaly, hypercalcemia, skin and lungs injuries.	(Shimoyama 1991)
The severity of ATLL sub-types	Intense and lymphoma sub-types are more extreme than smoldering and chronic sub-types	(Katsuya *et al.*, 2015)
Frequency of ATLL sub-types	The frequency of cute subtypes of ATLL and that of lymphoma subtypes are represented as 60% and 20% of all the subtypes respectively.	(Mehta-Shah *et al.*, 2017)
Morphology of Leukemic cells	Uncommon with flower-shaped nuclei	(Uchiyama 1997)
Phenotypic markers	All the C-C chemokine receptor type-4 (CD2, CD4, CD3, CD25, CD5, CCR4) with exception of CD7 are found to be down-regulated in those cells which remain suffering from an infection of HTLV-1 that suggests the disease progression over a time period of infection state.	(Kagdi *et al.*, 2017; Kobayashi *et al.*, 2014)
Biomarkers for tax of ATLL sickness movement	Exponential expression of Cell Adhesion Molecule-1 (CADM1) on ATLL cells unravels the huge impact on the process such as inter-cellular adhesion, tissue invasion and finally development of tumors.	(Nakahata and Morishita 2012)
Marker of ATLL sub-type aggressiveness	Aggressive subtypes of ATLL express C-C chemokine receptor type 7 (CCR7) receptor. Expression of the presence of CCR7 is an indicator of the aggressiveness of ATLL.	(Kagdi et al., 2017)

Tax protein has been considered for a long time to be the sole oncogenic factor for the malignant change of the cells having infection of HTLV-1 but in the ongoing years, different investigations have proposed that HBZ is progressively a basic oncogenic factor in the transformation of the infected cell to malignant cells. Transducing Tax-expression vectors mediated in vitro immortalization of T-cell(Akagi *et al.*, 1995), in vivo transgenic expression of tax-induced cancer, expression of tax by a natural killer cells tumour, induced by the granzyme B promotor(Grossman *et al.*, 1995) and the expression of pX triggered by H-2kd promoter which is responsible for causing breast cancer(Shikishima *et al.*, 1997), are the solid confirmations recommending that the high level of expression or insistent expression of tax protein is an oncogenic factor. Different investigations on HTLV-1 proviruses and viral gene transcripts demonstrated ATLL cells hadn't demonstrated any expression of tax in about half of the aggregate instances of ATLL while expression of HBZ has been recorded in all the cases of ATL which emphatically confirms the irreplaceable role of HBZ in malignant transformation. Development of

T-cell lymphoma by means of HBZ transgenic suggests a significant role of HBZ in the cellular transformation mechanism which is dependent on HTLV-1 infection(Satou *et al.,* 2011). HTLV-1 induced leukemogenesis is a multi-factorial phenomenon that encompasses various mechanisms such as up-regulated and down-regulated action of different micro-RNAs, differential expression of mRNA, alteration of Cellular signalling, somatic mutations, aneuploidy and epigenetic deregulation that transforms the infected cells to malignant cells(Watanabe 2017). The noteworthy job of tax protein has been entrenched in these procedures, for example, expression modulation of both cellular and viral genes by means of activation of cAMP response element-binding protein (CREB) or Activating transcription factor (ATF), serum response factor (SRF) as well as nuclear factor-kappa B (NF-κB)-dependent vital pathway(Currer *et al.,* 2012), by preventing cellular cycle seizure, hindering both DNA damage repair as well as apoptosis pathways. These factors evidently emphasize the role of tax in the proliferation of cells with infection as well as in the building-up of genetic alteration. Tax induces transformation of rodent fibroblast(Tanaka *et al.,* 1990), in transgenic Drosophila melanogaster and mice as well(Niewiesk 2016), while weakly transforms human T-cell (Bellon *et al.,* 2010), suggesting a significant role of tax in transformation.

Transcription of HBZ gene communicates in every one of the instances of ATLL(Satou et al., 2006) and the result of HBZ gene expression supports the proliferation of T-cells, smothers transcription process mediated by tax protein via 5' LTR, hampers NF-κB activity, interfere apoptosis and autophagy, causes disruption of the very integrity of the host genome through miRNA expression and triggers impairment of TH1-mediated immune response against the virus(Ma *et al.,* 2016). Aside from Apart from the above-mentioned functions of HTLV-1-infected cell persistence, HTLV-1-induced transformation is also facilitated by HBZ while its role in HTLV-1 replication has not been observed. Thus, the synergistic and cooperative role of both tax as well as HBZ in the cancerous transformation of CD4+ T-lymphocytes has been well established and in fact induction of T-cells to be Tregs by HBZ expression (mainly by up-regulating Foxp3 expression) has been reported(Yamamoto-Taguchi *et al.,* 2013). Tax expression immortalizes and changes human CD4+ Foxp3+ cells(Chen *et al.,* 2015), which shows that Tax oncogenic features in human cells may also necessitate a minimum HBZ activity. Decontrolled immune response for the most part by means of tolerogenic state enlistment has been recorded as an additional factor(Kannagi *et al.,* 2012). A tolerogenic state is accomplished through the direct impact of Interleukin-10 (Mori *et al.,* 1996) and Transforming growth factor-beta (TGF-β)(Niitsu *et al.,* 1988) generated by infected cells. It is also achieved through the indirect activity of C-C theme chemokine ligand 22 (CCL22) produced by cells having an infection of HTLV-1(Toulza *et al.,* 2010). Once the tolerogenic state is achieved it leads to the employment of regulatory T-lymphocytes and the hanging-up of the response of HTLV-1-specific cytotoxic T-lymphocytes(Bangham and Toulza 2011) (**Figure 3**). Inactivation of the expression of tax gene is achieved by three different mechanisms such as nonsense mutation, DNA methylation at a position of 5'LTR and deletion of the 5'LTR region. DNA methylation at 5'LTR which gets mounted up amid the natural progression of infection, but not to the degree of pX and 3'LTR(Taniguchi *et al.,* 2005), prompts the silencing of the sense strand transcription from the 5'LTR(Koiwa *et al.,* 2002). The CTCF-restricting region in pX area (Fig. 1) that was recently revealed, may account for the complete stoppage of DNA methylation process preceding the pX as well as 3'LTR to safeguard the sustained expression of HBZ(Satou *et al.,* 2016) as the pX and

3'LTR are the basic factor for HBZ transcription. Malignant ATLL clones in various cases display mutations in tax(Takeda *et al.,* 2004) and hypermethylation or deletion of 5'LTR, leading to the generation of defective provirus (defective provirus type-2) prior to the integration of the provirus into the genome (Koiwa et al., 2002). Since the initiation of transcription of viral genes is caused by 5'LTR (encoded by positive-strand including tax) therefore, the absence of 5'LTR disallows the expression of tax gene in many instances of ATLL (Fig. 3b). Tax gene nonsense mutation (observed in about ten percent of the cases of ATLL) are observed in asymptomatic carrier which is produced during reverse transcription in provirus in APOBEC3G target sequence(Fan *et al.,* 2010). In light of this perception, it is reasoned that the nonsense mutations are generated prior to infection, and the mutated tax gene (nonsense) carrying infected cells gets changed into ATLL cells which clearly demonstrates that HBZ plays an essential job in the process of oncogenesis. An obligatory long period of latency dormancy for initiation of ATLL demonstrates that mounting up of various levels of genetic and epigenetic alteration in the genes that are allied with the particular pathways which target tax as well as HBZ, is necessary for the development of ATLL (figure 2)(Kataoka *et al.,* 2015). CCR4 gene Gain-of-function mutations (GOFM) have been found to be connected to the proliferation and infiltration of ATLL cells (Kataoka et al., 2015). NfkB augmentation in ATLL cells even in the absence of expression of tax by miR31 has been explained(Yamagishi *et al.,* 2012). These viral proteins and mutations might be focused on therapeutic value in instances of ATLL. Notwithstanding the highly immunogenic nature(Kannagi *et al.,* 1992) of tax, the absence of its expression in most ATLL cells supports the evasion from tax-specific cytotoxic T-lymphocyte immune response in the patient suffering from ATLL. VHTL-1 is a human oncogenic infection as its regulatory proteins (tax and HBZ) indicate a tremendous amount of oncogenic features that assume a significant role in the development of cancer. HTLV-1 oncogenesis progression necessitates the micro-environment alteration, course of chronic infection, evasion from host immune response and controlled inflammatory response (reason for immunosuppression)(Virgin *et al.,* 2009).

Mechanism of TSP/HAM Progression:

It is a chronic inflammatory-related disease of CNS (central nervous system) that advances in about 1-2% of the infected individuals with certain specific characteristic clinical features (lower limb progressive spastic weakness, lower back pain, dysfunction of bladder and bowel). It results from disadvantageous interaction between CNS and our immune system. Based on the fact that about 60% of the TSP patients were found to show seropositivity for various antigens of the HTLV-1 virus, the causal relationship between the virus and STP was established(Gessain et al., 1985**).** HTLV-1 was found to have a causative association with HAM(Osame *et al.,* 1986), later on, it was likewise explored that the TSP and HAM had a similar infection condition, and thus the condition was named TSP/HAM. Cytopathic effect of viruses and/or immune reaction (Interferon gamma generated by cells infected with HTLV-1 and HTLV-1 specific CTLs infiltration in the cerebrospinal fluid) causes damage to neural tissue (loss of spinal cord myelin sheath and characteristic lesion in the spinal cord). HTLV-1-infected astrocytes trigger the release of neural tissue damaging pro-inflammatory cytokines (inflammatory mediators) that play a vital role in disease development. Mounting up of the HTLV-1 CTLs in the CSF-cerebrospinal fluid and inflammatory products like IFN-γ (Interferon gamma) released by them results in the damage of neighbouring neurons, glial cells and astrocytes(Nagai et al., 2001) **(**Fig. 3a**).** The ambiguous role of HTLV-1-specific cytotoxic T-cells invaded in CSF has been

recorded as it causes infected cell killing, however on the other hand because of chronic inflammatory cytokines generation, severe tissue damage has been noticed too. Infected CD4+ T-cells mounted up in CSF of patients have also shown the capability of releasing IFN-γ. C-X-C motif chemokine ligand 10 designated as CXCL10 (an inflammatory cytokine) secreted by astrocytes under the activating influence of IFN-γ which supports the homing of leukocytes to inflamed tissues and thus, leading to the augmentation of the infiltration in the cerebrospinal fluid of both virus-specific CTLs as well as infected CD4+ T-lymphocytes in a manner of + feedback loop(Yamano and Coler-Reilly 2017) **(**Fig. 3a**).** People with the HLA-A*02 allele and HLA-B*54 allele of (human leukocyte antigen) class-1 genotype particularity display lower (higher HTLV-1 specific CTL response) and higher hazard (lower HTLV-1 specific CTL response) of creating TSP/HAM individually(Bangham *et al.,* 2015). The beneficial antiviral activity of type-1 IFAN in case of HTLV-1 infection process and disease development may be debated as an IFN-inducible signature has been noted in all immune (blood) cells of patients suffering from TSP/HAM, which is indicative of in vivo multifaceted deregulation of IFN production, resulting in the disease progression as opposing to the protective role against viral infection (Tattermusch *et al.*, 2012).

HTLV-1 Related Other Diseases and Disorders:

Various ailments and disorders, for example, uveitis, conjunctivitis, interstitial keratitis, infective dermatitis, myositis, joint inflammation, aspiratory ailments, Sjogren's syndrome, sicca disorder, Graves' malady, Hashimoto's thyroiditis, and polyneuropathies have been seen in both bearer and patients of TSP/HAM or ATLL(Gonçalves et al., 2010; Kamoi and Mochizuki 2012). Crusted scabies, Strongyloides stercoralis, tuberculosis and leprosy have been seen as opportunistic infection in patients experiencing ATLL(McKendall 2014).

Conclusion

Since the discovery of HTLV-1, its characterization has permitted significant breakthroughs in the area of cellular signalling as well as immunology but effective treatment, mainly due to the lack of prophylactic vaccine development against HTLV-1 hasn't been yet achieved. Numerous investigations associated with the viral cycle, diseases and management of patients have been observed to be extraordinarily advantageous in recent years. Advancement and progress are required for a better understanding and learning of the mechanisms related to viral persistence, pathogenesis and oncogenesis.

Funding:

The author extends their appreciation to the Deputyship for Research and Innovation, Ministry of Education in Saudi Arabia for funding this research work through project number MOE- BU- 1- 2020

Conflict of interest:

The author declares no conflicts of interest.

REFERENCES

Akagi T, Ono H, Shimotohno K. (1995). Characterization of T cells immortalized by Tax1 of human T-cell leukemia virus type 1. *Blood,* 86:4243-9.

Alais S, Mahieux R, Dutartre H. (2015). Viral Source-Independent High Susceptibility of Dendritic Cells to Human T-Cell Leukemia Virus Type 1 Infection Compared to That of T Lymphocytes. *Journal of Virology,* 89:10580-90.

Albrecht B, Collins ND, Burniston MT, Nisbet JW, Ratner L, Green PL, Lairmore MD. (2000). Human T-lymphotropic virus type 1 open reading frame I p12(I) is required for efficient viral infectivity in primary lymphocytes. *Journal of Virology,* 74:9828-35.

Alvarez C, Gotuzzo E, Vandamme AM, Verdonck K. (2016). Family

````
````

Aggregation of Human T-Lymphotropic Virus 1-Associated Diseases: A Systematic Review. *Frontiers in microbiology*, 7:1674.

Arnold J, Zimmerman B, Li M, Lairmore MD, Green PL. (2008). Human T-cell leukemia virus type-1 antisense-encoded gene, Hbz, promotes T-lymphocyte proliferation. *Blood*, 112:3788-97.

Bangham CR, Araujo A, Yamano Y, Taylor GP. (2015). HTLV-1-associated myelopathy/tropical spastic paraparesis. *Nature Reviews Disease Primers*, 1:15012.

Bangham CR, Cook LB, Melamed A. (2014). HTLV-1 clonality in adult T-cell leukaemia and non-malignant HTLV-1 infection. *Seminars in cancer biology*, 26:89-98.

Bangham CR, Toulza F. (2011). Adult T cell leukemia/lymphoma: FoxP3+ cells and the cell-mediated immune response to HTLV-1. In *Advances in cancer research*. Elsevier. pp 163-182.

Baratella M, Forlani G, Raval GU, Tedeschi A, Gout O, Gessain A, Tosi G, Accolla RS. (2017). Cytoplasmic localization of HTLV-1 HBZ protein: a biomarker of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *PLoS neglected tropical diseases*, 11:e0005285.

Barré-Sinoussi F, Chermann J-C, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science,* 220: 868-871.

Basbous J, Arpin C, Gaudray G, Piechaczyk M, Devaux C, Mesnard J-M. (2003). The HBZ factor of human T-cell leukemia virus type I dimerizes with transcription factors JunB and c-Jun and modulates their transcriptional activity. *Journal of Biological Chemistry,* 278:43620-43627.

Bellon M, Baydoun HH, Yao Y, Nicot C. (2010). HTLV-I Tax-dependent and-independent events associated with immortalization of human primary T lymphocytes. *Blood,* 115:2441-2448.

Belrose G, Gross A, Olindo S, Lézin A, Dueymes M, Komla-Soukha I, Smadja D, Tanaka Y, Willems L, Mesnard J-M. (2011). Effects of valproate on Tax and HBZ expression in HTLV-1 and HAM/TSP T lymphocytes. *Blood,* 118:2483-2491.

Bertotto A, Gerli R, Fabietti G, Crupi S, Arcangeli C, Scalise F, Vaccaro R. (1990). Human breast milk T lymphocytes display the phenotype and functional characteristics of memory T cells. *European journal of immunology,* 20:1877-1880.

Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L and others. (2009). A review of human carcinogens--Part B: biological agents. *The Lancet Oncology*, 10:321-2.

Cann AJ, Rosenblatt JD, Wachsman W, Shah NP, Chen IS. (1985). Identification of the gene responsible for human T-cell leukaemia virus transcriptional regulation. *Nature*, 318:571-4.

Cavrois M, Gout O, Gessain A, Wain-Hobson S, Wattel E. (1998). Persistent oligoclonal expansion of human T-cell leukemia virus type 1-infected circulating cells in patients with Tropical spastic paraparesis /HTLV-1 associated myelopathy. *Oncogene*,17:77.

Chen L, Liu D, Zhang Y, Zhang H, Cheng H. (2015). Foxp3-dependent transformation of human primary CD4+ T lymphocytes by the retroviral protein tax. *Biochemical*

and biophysical research communications, 466:523-529.

Chevalier SA, Durand S, Dasgupta A, Radonovich M, Cimarelli A, Brady JN, Mahieux R, Pise-Masison CA. (2012). The transcription profile of Tax-3 is more similar to Tax-1 than Tax-2: insights into HTLV-3 potential leukemogenic properties. *PLoS One,* 7:e41003.

Clerc I, Polakowski N, Andre-Arpin C, Cook P, Barbeau B, Mesnard JM, Lemasson I. (2008). An interaction between the human T cell leukemia virus type 1 basic leucine zipper factor (HBZ) and the KIX domain of p300/CBP contributes to the down-regulation of tax-dependent viral transcription by HBZ. *The Journal of biological chemistry,* 283:23903-13.

Collins ND, Newbound GC, Albrecht B, Beard JL, Ratner L, Lairmore MD. (1998). Selective ablation of human T-cell lymphotropic virus type 1 p12I reduces viral infectivity in vivo. *Blood,* 91:4701-7.

Cook L, Melamed A, Yaguchi H, Bangham CR. (2017). The impact of HTLV-1 on the cellular genome. *Current opinion in virology,* 26:125-131.

Currer R, Van Duyne R, Jaworski E, Guendel I, Sampey G, Das R, Narayanan A, Kashanchi F. (2012). HTLV tax: a fascinating multifunctional co-regulator of viral and cellular pathways. *Front Microbiol,* 3:406.

de Castro-Amarante MF, Pise-Masison CA, McKinnon K, Washington Parks R, Galli V, Omsland M, Andresen V, Massoud R, Brunetto G, Caruso B and others. (2015). Human T Cell Leukemia Virus Type 1 Infection of the Three Monocyte Subsets Contributes to Viral Burden in Humans. *Journal of Virology,* 90:2195-207.

Demontis MA, Sadiq MT, Golz S, Taylor GP. (2015). HTLV-1 viral RNA is detected rarely in plasma of HTLV-1 infected subjects. *Journal of medical virology,* 87:2130-4.

Derse D, Hill SA, Lloyd PA, Chung H, Morse BA. (2001). Examining human T-lymphotropic virus type 1 infection and replication by cell-free infection with recombinant virus vectors. *Journal of Virology,* 75:8461-8.

Dutartre H, Claviere M, Journo C, Mahieux R. (2016). Cell-Free versus Cell-to-Cell Infection by Human Immunodeficiency Virus Type 1 and Human T-Lymphotropic Virus Type 1: Exploring the Link among Viral Source, Viral Trafficking, and Viral Replication. *Journal of Virology,* 90:7607-17.

Fan J, Ma G, Nosaka K, Tanabe J, Satou Y, Koito A, Wain-Hobson S, Vartanian JP, Matsuoka M. (2010). APOBEC3G generates nonsense mutations in human T-cell leukemia virus type 1 proviral genomes in vivo. Journal of Virology, 84:7278-87.

Felber BK, Paskalis H, Kleinman-Ewing C, Wong-Staal F, Pavlakis GN. (1985). The pX protein of HTLV-I is a transcriptional activator of its long terminal repeats. *Science,* 229:675-9.

Gallo RC. (2005). History of the discoveries of the first human retroviruses: HTLV-1 and HTLV-2. *Oncogene,* 24:5926-30.

Gazon H, Barbeau B, Mesnard J-M, Peloponese Jr J-M. (2018). Hijacking of the AP-1 Signaling Pathway during Development of ATL. *Frontiers in microbiology,* 8:2686.

Gazon H, Lemasson I, Polakowski N, Césaire R, Matsuoka M, Barbeau B, Mesnard J-M, Peloponese J-M. (2012). Human T-cell leukemia virus type 1 (HTLV-1) bZIP factor requires cellular transcription factor JunD to upregulate HTLV-1

antisense transcription from the 3′ long terminal repeat. *Journal of Virology*, 86:9070-9078.

Gessain A, Cassar O. (2012). Epidemiological aspects and world distribution of HTLV-1 infection. *Frontiers in microbiology*, 3:388.

Gessain A, Vernant J, Maurs L, Barin F, Gout O, Calender Ad, De Thé G. (1985). Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *The Lancet*, 326:407-410.

Gillet NA, Malani N, Melamed A, Gormley N, Carter R, Bentley D, Berry C, Bushman FD, Taylor GP, Bangham CR. (2011). The host genomic environment of the provirus determines the abundance of HTLV-1–infected T-cell clones. *Blood*, 117:3113-3122.

Gonçalves DU, Proietti FA, Ribas JGR, Araújo MG, Pinheiro SR, Guedes AC, Carneiro-Proietti ABF. (2010). Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clinical microbiology reviews*, 23:577-589.

Goon PK, Igakura T, Hanon E, Mosley AJ, Barfield A, Barnard AL, Kaftantzi L, Tanaka Y, Taylor GP, Weber JN and others. (2004). Human T cell lymphotropic virus type I (HTLV-I)-specific CD4+ T cells: immunodominance hierarchy and preferential infection with HTLV-I. *Journal of immunology*, (Baltimore, Md. : 1950) 172:1735-43.

Grassmann R, Aboud M, Jeang KT. (2005). Molecular mechanisms of cellular transformation by HTLV-1 Tax. *Oncogene*, 24:5976-85.

Grassmann R, Berchtold S, Radant I, Alt M, Fleckenstein B, Sodroski JG, Haseltine WA, Ramstedt U. (1992). Role of human T-cell leukemia virus type 1 X region proteins in immortalization of primary human lymphocytes in culture. *Journal of Virology*, 66:4570-5.

Gross C, Thoma-Kress AK. (2016). Molecular Mechanisms of HTLV-1 Cell-to-Cell Transmission. *Viruses*, 8:74.

Grossman WJ, Kimata JT, Wong FH, Zutter M, Ley TJ, Ratner L. (1995). Development of leukemia in mice transgenic for the tax gene of human T-cell leukemia virus type I. *Proceedings of the National Academy of Sciences of the United States of America* 92:1057-61.

Hasegawa H, Sawa H, Lewis MJ, Orba Y, Sheehy N, Yamamoto Y, Ichinohe T, Tsunetsugu-Yokota Y, Katano H, Takahashi H and others. (2006). Thymus-derived leukemia-lymphoma in mice transgenic for the Tax gene of human T-lymphotropic virus type I. *Nature medicine*, 12:466-72.

Hilburn S, Rowan A, Demontis MA, MacNamara A, Asquith B, Bangham CR, Taylor GP. (2011). In vivo expression of human T-lymphotropic virus type 1 basic leucine-zipper protein generates specific CD8+ and CD4+ T-lymphocyte responses that correlate with clinical outcome. *The Journal of infectious diseases*, 203:529-36.

Hino S. (2011). Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL Prevention Program Nagasaki. *Proceedings of the Japan Academy. Series B, Physical and biological sciences*, 87:152-66.

Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, Shirakawa S, Miyoshi I. (1981). Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proceedings of the National*

Academy of Sciences of the United States of America, 78:6476-80.

Hivin P, Frederic M, Arpin-Andre C, Basbous J, Gay B, Thebault S, Mesnard JM. (2005). Nuclear localization of HTLV-I bZIP factor (HBZ) is mediated by three distinct motifs. *Journal of cell science,* 118:1355-62.

Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, Tanaka Y, Osame M, Bangham CR. (2003). Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. *Science,* 299:1713-6.

Inoue J, Yoshida M, Seiki M. (1987). Transcriptional (p40x) and post-transcriptional (p27x-III) regulators are required for the expression and replication of human T-cell leukemia virus type I genes. *Proceedings of the National Academy of Sciences of the United States of America,* 84:3653-7.

Iwanaga R, Ohtani K, Hayashi T, Nakamura M. (2001). Molecular mechanism of cell cycle progression induced by the oncogene product Tax of human T-cell leukemia virus type I. *Oncogene,* 20:2055-67.

Jacobson S, Shida H, McFarlin DE, Fauci AS, Koenig S. (1990). Circulating CD8+ cytotoxic T lymphocytes specific for HTLV-I pX in patients with HTLV-I associated neurological disease. *Nature,* 348:245-8.

Jain P, Manuel SL, Khan ZK, Ahuja J, Quann K, Wigdahl B. (2009). DC-SIGN mediates cell-free infection and transmission of human T-cell lymphotropic virus type 1 by dendritic cells. *Journal of Virology,* 83:10908-21.

Jones KS, Petrow-Sadowski C, Huang YK, Bertolette DC, Ruscetti FW. (2008). Cell-free HTLV-1 infects dendritic cells leading to transmission and transformation of CD4(+) T cells. *Nature medicine,* 14:429-36.

Kagdi HH, Demontis MA, Fields PA, Ramos JC, Bangham CR, Taylor GP. (2017). Risk stratification of adult T-cell leukemia/lymphoma using immunophenotyping. *Cancer medicine,* 6:298-309.

Kamoi K, Mochizuki M. (2012). HTLV-1 uveitis. *Frontiers in* Microbiology**,** 3:270.

Kannagi M, Harada S, Maruyama I, Inoko H, Igarashi H, Kuwashima G, Sato S, Morita M, Kidokoro M, Sugimoto M and others. (1991). Predominant recognition of human T cell leukemia virus type I (HTLV-I) pX gene products by human CD8+ cytotoxic T cells directed against HTLV-I-infected cells. *International immunology,* 3:761-7.

Kannagi M, Hasegawa A, Takamori A, Kinpara S, Utsunomiya A. (2012). The roles of acquired and innate immunity in human T-cell leukemia virus type 1-mediated diseases. *Frontiers in* Microbiology**,** 3:323.

Kannagi M, Shida H, Igarashi H, Kuruma K, Murai H, Aono Y, Maruyama I, Osame M, Hattori T, Inoko H and others. (1992). Target epitope in the Tax protein of human T-cell leukemia virus type I recognized by class I major histocompatibility complex-restricted cytotoxic T cells. *Journal of Virology,* 66:2928-33.

Kaplan JE, Khabbaz RF, Murphy EL, Hermansen S, Roberts C, Lal R, Heneine W, Wright D, Matijas L, Thomson R and others. (1996). Male-to-female transmission of human T-cell lymphotropic virus types I and II: association with viral load. The Retrovirus Epidemiology Donor Study Group. Journal of acquired immune deficiency syndromes and human retrovirology : *official publication of the*

International Retrovirology Association, 12:193-201.

Kashanchi F, Brady JN. (2005). Transcriptional and post-transcriptional gene regulation of HTLV-1. *Oncogene*, 24:5938-51.

Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G and others. (2015). Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nature genetics*, 47:1304-15.

Katsuya H, Ishitsuka K, Utsunomiya A, Hanada S, Eto T, Moriuchi Y, Saburi Y, Miyahara M, Sueoka E, Uike N and others. (2015). Treatment and survival among 1594 patients with ATL. *Blood*, 126:2570-7.

Keele BF, Van Heuverswyn F, Li Y, Bailes E, Takehisa J, Santiago ML, Bibollet-Ruche F, Chen Y, Wain LV, Liegeois F and others. (2006). Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science*, 313:523-6.

Kinosada H, Yasunaga JI, Shimura K, Miyazato P, Onishi C, Iyoda T, Inaba K, Matsuoka M. (2017). HTLV-1 bZIP Factor Enhances T-Cell Proliferation by Impeding the Suppressive Signaling of Co-inhibitory Receptors. *Plos Pathogens*,13:e1006120.

Kirk PD, Huvet M, Melamed A, Maertens GN, Bangham CR. (2016). Retroviruses integrate into a shared, non-palindromic DNA motif. *Nature microbiology*, 2:16212.

Kobayashi S, Nakano K, Watanabe E, Ishigaki T, Ohno N, Yuji K, Oyaizu N, Asanuma S, Yamagishi M, Yamochi T and others. (2014). CADM1 expression and stepwise downregulation of CD7 are closely associated with clonal expansion of HTLV-I-infected cells in adult T-cell leukemia/lymphoma. Clinical cancer research : *an official journal of the American Association for Cancer Research*, 20:2851-61.

Koiwa T, Hamano-Usami A, Ishida T, Okayama A, Yamaguchi K, Kamihira S, Watanabe T. (2002). 5'-long terminal repeat-selective CpG methylation of latent human T-cell leukemia virus type 1 provirus in vitro and in vivo. *Journal of Virology*, 76:9389-97.

Koyanagi Y, Itoyama Y, Nakamura N, Takamatsu K, Kira J, Iwamasa T, Goto I, Yamamoto N. (1993). In vivo infection of human T-cell leukemia virus type I in non-T cells. *Virology*, 196:25-33.

Lee T, Coligan J, Homma T, McLane M, Tachibana N, Essex M. (1984). Human T-cell leukemia virus-associated membrane antigens: identity of the major antigens recognized after virus infection. *Proceedings of the National Academy of Sciences*, 81:3856-3860.

Leung K, Nabel GJ. (1988). HTLV-1 transactivator induces interleukin-2 receptor expression through an NF-kappa B-like factor. *Nature*, 333:776-8.

Ma G, Yasunaga J-i, Akari H, Matsuoka M. (2015). TCF1 and LEF1 act as T-cell intrinsic HTLV-1 antagonists by targeting Tax. *Proceedings of the National Academy of Sciences*, 112:2216-2221.

Ma G, Yasunaga J-i, Matsuoka M. (2016). Multifaceted functions and roles of HBZ in HTLV-1 pathogenesis. *Retrovirology*, 13:16.

Maertens GN. (2015). B′-protein phosphatase 2A is a functional binding partner of delta-retroviral integrase. *Nucleic acids research*, 44:364-376.

Mahgoub M, Yasunaga J-i, Iwami S, Nakaoka S, Koizumi Y, Shimura K, Matsuoka M. (2018). Sporadic on/off switching of HTLV-1 Tax expression is crucial to maintain the

whole population of virus-induced leukemic cells. *Proceedings of the National Academy of Sciences*, 115:E1269-E1278.

Majorovits E, Nejmeddine M, Tanaka Y, Taylor GP, Fuller SD, Bangham CR. (2008). Human T-lymphotropic virus-1 visualized at the virological synapse by electron tomography. *PloS one*, 3:e2251.

Martin F, Castro H, Gabriel C, Adonis A, Fedina A, Harrison L, Brodnicki L, Demontis MA, Babiker AG, Weber JN. (2012). Ciclosporin A proof of concept study in patients with active, progressive HTLV-1 associated myelopathy/tropical spastic paraparesis. *PLoS neglected tropical diseases*, 6:e1675.

Matsuoka M, Jeang K-T. (2007). Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nature Reviews Cancer*, 7:270.

Mazurov D, Ilinskaya A, Heidecker G, Lloyd P, Derse D. (2010). Quantitative comparison of HTLV-1 and HIV-1 cell-to-cell infection with new replication dependent vectors. *Plos Pathogens*, 6:e1000788.

McKendall RR. (2014). Neurologic disease due to HTLV-1 infection. In *Handbook of clinical neurology*. Elsevier. pp 507-530.

Mehta-Shah N, Ratner L, Horwitz SM. (2017). Adult T-Cell Leukemia/ Lymphoma. *Journal of oncology practice*, 13:487-492.

Melamed A, Laydon DJ, Al Khatib H, Rowan AG, Taylor GP, Bangham CR. (2015). HTLV-1 drives vigorous clonal expansion of infected CD8+ T cells in natural infection. *Retrovirology*, 12:91.

Melamed A, Laydon DJ, Gillet NA, Tanaka Y, Taylor GP, Bangham CR. (2013). Genome-wide determinants of proviral targeting, clonal abundance and expression in natural HTLV-1 infection. *PLoS pathogens*, 9:e1003271.

Mori N, Gill P, Mougdil T, Murakami S, Eto S, Prager D. (1996). Interleukin-10 gene expression in adult T-cell leukemia. *Blood*, 88:1035-1045

Mulloy J, Kislyakova T, Cereseto A, Casareto L, LoMonico A, Fullen J, Lorenzi M, Cara A, Nicot C, Giam C-Z. (1998). Human T-cell lymphotropic/leukemia virus type 1 Tax abrogates p53-induced cell cycle arrest and apoptosis through its CREB/ATF functional domain. *Journal of Virology*, 72:8852-8860.

Murphy EL. (2016). Infection with human T-lymphotropic virus types-1 and -2 (HTLV-1 and -2): Implications for blood transfusion safety. Transfusion clinique et biologique : *journal de la Societe francaise de transfusion sanguine*, 23:13-9.

Nagai M, Brennan MB, Sakai JA, Mora CA, Jacobson S. (2001). CD8+ T cells are an in vivo reservoir for human T-cell lymphotropic virus type I. *Blood*, 98:1858-1861.

Nakahata S, Morishita K. (2012). CADM1/TSLC1 is a novel cell surface marker for adult T-cell leukemia/lymphoma. *Journal of Clinical and Experimental Hematopathology*, 52:17-22.

Nam SH, Kidokoro M, Shida H, Hatanaka M. (1988). Processing of gag precursor polyprotein of human T-cell leukemia virus type I by virus-encoded protease. *Journal of Virology*, 62:3718-28.

Nejmeddine M, Bangham CR. (2010). The HTLV-1 virological synapse. *Viruses*, 2:1427-1447.

Nejmeddine M, Barnard AL, Tanaka Y, Taylor GP, Bangham CR. (2005). Human T-lymphotropic virus, type 1, tax protein triggers microtubule reorientation in the virological synapse. *The Journal of biological chemistry*, 280:29653-60.

````
````

Nicot C, Harrod RL, Ciminale V, Franchini G. (2005). Human T-cell leukemia/lymphoma virus type 1 nonstructural genes and their functions. *Oncogene*, 24:6026-34.

Niewiesk S. (2016). Animals Models of Human T Cell Leukemia Virus Type I Leukemogenesis. *ILAR journal*, 57:3-11.

Niitsu Y, Urushizaki Y, Koshida Y, Terui K, Mahara K, Kohgo Y, Urushizaki I. (1988). Expression of TGF-beta gene in adult T cell leukemia. *Blood*, 71:263-6.

Nyambi PN, Ville Y, Louwagie J, Bedjabaga I, Glowaczower E, Peeters M, Kerouedan D, Dazza M-C, Larouzé B, van der Groen G and others. (1996). Mother-to-Child Transmission of Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/II) in Gabon: A Prospective Follow-up of 4 Years. *JAIDS Journal of Acquired Immune Deficiency Syndromes* ,12:187-192.

Nyborg JK, Egan D, Sharma N. (2010). The HTLV-1 Tax protein: revealing mechanisms of transcriptional activation through histone acetylation and nucleosome disassembly. *Biochimica et biophysica acta*, 1799:266-74.

Okamoto K, Fujisawa J, Reth M, Yonehara S. (2006). Human T-cell leukemia virus type-I oncoprotein Tax inhibits Fas-mediated apoptosis by inducing cellular FLIP through activation of NF-kappaB. Genes to cells : *devoted to molecular & cellular mechanisms*, 11:177-191.

Osame M, Janssen R, Kubota H, Nishitani H, Igata A, Nagataki S, Mori M, Goto I, Shimabukuro H, Khabbaz R and others. (1990). Nationwide survey of HTLV-I-associated myelopathy in Japan: association with blood transfusion. *Annals of neurology*, 28:50-6.

Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M. (1986). HTLV-I associated myelopathy, a new clinical entity. *Lancet (London, England)*, 1:1031-2.

Overbaugh J, Bangham CR. (2001). Selection forces and constraints on retroviral sequence variation. *Science*, 292:1106-9.

Paine E, Gu R, Ratner L. (1994). Structure and expression of the human T-cell leukemia virus type 1 envelope protein. *Virology*, 199:331-8.

Pais-Correia AM, Sachse M, Guadagnini S, Robbiati V, Lasserre R, Gessain A, Gout O, Alcover A, Thoulouze MI. (2010). Biofilm-like extracellular viral assemblies mediate HTLV-1 cell-to-cell transmission at virological synapses. *Nature medicine*, 16:83-9.

Panfil AR, Dissinger NJ, Howard CM, Murphy BM, Landes K, Fernandez SA, Green PL. (2016). Functional Comparison of HBZ and the Related APH-2 Protein Provides Insight into Human T-Cell Leukemia Virus Type 1 Pathogenesis. *Journal of Virology*, 90:3760-72.

Peloponese JM, Jr., Jeang KT. (2006). Role for Akt/protein kinase B and activator protein-1 in cellular proliferation induced by the human T-cell leukemia virus type 1 tax oncoprotein. *The Journal of biological chemistry*, 281:8927-38.

Pique C, Jones KS. (2012). Pathways of cell-cell transmission of HTLV-1. *Frontiers in* Microbiology**,** 3:378.

Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. (1980). Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proceedings of the National Academy of Sciences of the United States of America* ,77:7415-9.

Richardson JH, Edwards AJ, Cruickshank JK, Rudge P, Dalgleish AG. (1990). In vivo cellular tropism of human T-

cell leukemia virus type 1. *Journal of Virology*, 64:5682-7.

Rizkallah G, Alais S, Futsch N, Tanaka Y, Journo C, Mahieux R, Dutartre H. (2017). Correction: Dendritic cell maturation, but not type I interferon exposure, restricts infection by HTLV-1, and viral transmission to T-cells. *Plos Pathogens,*13:e1006494.

Robek MD, Ratner L. (1999). Immortalization of CD4(+) and CD8(+) T lymphocytes by human T-cell leukemia virus type 1 Tax mutants expressed in a functional molecular clone. *Journal of Virology*, 73:4856-65.

Ross TM, Narayan M, Fang ZY, Minella AC, Green PL. (2000). Human T-cell leukemia virus type 2 tax mutants that selectively abrogate NFkappaB or CREB/ATF activation fail to transform primary human T cells. *Journal of Virology*, 74:2655-62.

Satake M, Iwanaga M, Sagara Y, Watanabe T, Okuma K, Hamaguchi I. (2016). Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: a nationwide retrospective cohort analysis. *The Lancet. Infectious diseases*, 16:1246-1254.

Satou Y, Miyazato P, Ishihara K, Yaguchi H, Melamed A, Miura M, Fukuda A, Nosaka K, Watanabe T, Rowan AG and others. (2016). The retrovirus HTLV-1 inserts an ectopic CTCF-binding site into the human genome. *Proceedings of the National Academy of Sciences of the United States of America*, 113:3054-9.

Satou Y, Yasunaga J, Yoshida M, Matsuoka M. (2006). HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. *Proceedings of the National Academy of Sciences of the United States of America*, 103:720-5.

Satou Y, Yasunaga J, Zhao T, Yoshida M, Miyazato P, Takai K, Shimizu K, Ohshima K, Green PL, Ohkura N and others. (2011). HTLV-1 bZIP factor induces T-cell lymphoma and systemic inflammation in vivo. *Plos Pathogens,*7:e1001274.

Sherer NM, Lehmann MJ, Jimenez-Soto LF, Horensavitz C, Pypaert M, Mothes W. (2007). Retroviruses can establish filopodial bridges for efficient cell-to-cell transmission. *Nature cell biology*, 9:310-5.

Shikishima H, Ikeda H, Yamada S, Yamazaki H, Kikuchi K, Wakisaka A, Kasai N, Shimotono K, Yoshiki T. (1997). HTLV-I pX transgenic rats: development of cytokine-producing mammary carcinomas and establishment of the pX mammary carcinoma cell lines. *Leukemia*, 11 Suppl 3:70-2.

Shimoyama M. (1991). Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). *British journal of haematology*, 79:428-37.

Shinagawa M, Jinno-Oue A, Shimizu N, Roy BB, Shimizu A, Hoque SA, Hoshino H. (2012). Human T-cell leukemia viruses are highly unstable over a wide range of temperatures. *The Journal of general virology*, 93:608-17.

Sobata R, Matsumoto C, Uchida S, Suzuki Y, Satake M, Tadokoro K. (2015). Estimation of the infectious viral load required for transfusion-transmitted human T-lymphotropic virus type 1 infection (TT-HTLV-1) and of the effectiveness of leukocyte reduction in preventing TT-HTLV-1. *Vox sanguinis*, 109:122-8.

Southern SO, Southern PJ. (1998). Persistent HTLV-I infection of breast luminal epithelial cells: a role in HTLV transmission? *Virology*, 241:200-14.

````
````

Sugata K, Yasunaga J, Kinosada H, Mitobe Y, Furuta R, Mahgoub M, Onishi C, Nakashima K, Ohshima K, Matsuoka M. (2016). HTLV-1 Viral Factor HBZ Induces CCR4 to Promote T-cell Migration and Proliferation. *Cancer research*, 76:5068-79.

Takeda S, Maeda M, Morikawa S, Taniguchi Y, Yasunaga J, Nosaka K, Tanaka Y, Matsuoka M. (2004). Genetic and epigenetic inactivation of tax gene in adult T-cell leukemia cells. *International journal of cancer*, 109:559-67.

Tanaka-Nakanishi A, Yasunaga J, Takai K, Matsuoka M. (2014). HTLV-1 bZIP factor suppresses apoptosis by attenuating the function of FoxO3a and altering its localization. *Cancer research*, 74:188-200.

Tanaka A, Takahashi C, Yamaoka S, Nosaka T, Maki M, Hatanaka M. (1990). Oncogenic transformation by the tax gene of human T-cell leukemia virus type I in vitro. *Proceedings of the National Academy of Sciences of the United States of America*, 87:1071-5.

Taniguchi Y, Nosaka K, Yasunaga J, Maeda M, Mueller N, Okayama A, Matsuoka M. (2005). Silencing of human T-cell leukemia virus type I gene transcription by epigenetic mechanisms. *Retrovirology*, 2:64.

Tattermusch S, Skinner JA, Chaussabel D, Banchereau J, Berry MP, McNab FW, O'Garra A, Taylor GP, Bangham CR. (2012). Systems biology approaches reveal a specific interferon-inducible signature in HTLV-1 associated myelopathy. *Plos Pathogens*,8:e1002480.

Thebault S, Basbous J, Hivin P, Devaux C, Mesnard JM. (2004). HBZ interacts with JunD and stimulates its transcriptional activity. *FEBS letters*, 562:165-70.

Toulza F, Nosaka K, Tanaka Y, Schioppa T, Balkwill F, Taylor GP, Bangham CR. (2010). Human T-lymphotropic virus type 1-induced CC chemokine ligand 22 maintains a high frequency of functional FoxP3+ regulatory T cells. *Journal of immunology (Baltimore, Md. : 1950)*, 185:183-9.

Tsukasaki K, Tobinai K. (2012). Clinical Trials and Treatment of ATL. *Leukemia research and treatment*, 2012:101754.

Uchiyama T. (1997). Human T cell leukemia virus type I (HTLV-I) and human diseases. *Annual review of immunology*, 15:15-37.

Valeri VW, Hryniewicz A, Andresen V, Jones K, Fenizia C, Bialuk I, Chung HK, Fukumoto R, Parks RW, Ferrari MG and others. (2010). Requirement of the human T-cell leukemia virus p12 and p30 products for infectivity of human dendritic cells and macaques but not rabbits. *Blood*, 116:3809-17.

Van Prooyen N, Gold H, Andresen V, Schwartz O, Jones K, Ruscetti F, Lockett S, Gudla P, Venzon D, Franchini G. (2010). Human T-cell leukemia virus type 1 p8 protein increases cellular conduits and virus transmission. *Proceedings of the National Academy of Sciences of the United States of America*, 107:20738-43.

Vandamme AM, Salemi M, Desmyter J. (1998). The simian origins of the pathogenic human T-cell lymphotropic virus type I. *Trends in microbiology*, 6:477-83.

Vernin C, Thenoz M, Pinatel C, Gessain A, Gout O, Delfau-Larue MH, Nazaret N, Legras-Lachuer C, Wattel E, Mortreux F. (2014). HTLV-1 bZIP factor HBZ promotes cell proliferation and genetic instability by activating OncomiRs. *Cancer research*, 74:6082-93.

Virgin HW, Wherry EJ, Ahmed R. (2009). Redefining chronic viral infection. *Cell*, 138:30-50.

Watanabe T. (2017). Adult T-cell leukemia: molecular basis for clonal expansion and transformation of HTLV-1-infected T cells. *Blood,* 129:1071-1081.

Wiktor SZ, Pate EJ, Murphy EL, Palker TJ, Champegnie E, Ramlal A, Cranston B, Hanchard B, Blattner WA. (1993). Mother-to-child transmission of human T-cell lymphotropic virus type I (HTLV-I) in Jamaica: association with antibodies to envelope glycoprotein (gp46) epitopes. *Journal of acquired immune deficiency syndromes,* 6:1162-1167.

Yamagishi M, Nakano K, Miyake A, Yamochi T, Kagami Y, Tsutsumi A, Matsuda Y, Sato-Otsubo A, Muto S, Utsunomiya A and others. (2012). Polycomb-mediated loss of miR-31 activates NIK-dependent NF-kappaB pathway in adult T cell leukemia and other cancers. *Cancer cell*, 21:121-35.

Yamamoto-Taguchi N, Satou Y, Miyazato P, Ohshima K, Nakagawa M, Katagiri K, Kinashi T, Matsuoka M. (2013). HTLV-1 bZIP factor induces inflammation through labile Foxp3 expression. *Plos Pathogens*, 9:e1003630.

Yamano Y, Coler-Reilly A. (2017). HTLV-1 induces a Th1-like state in CD4(+)CCR4(+) T cells that produces an inflammatory positive feedback loop via astrocytes in HAM/TSP. *Journal of neuroimmunology*, 304:51-55.

Yamaoka S, Tobe T, Hatanaka M. (1992). Tax protein of human T-cell leukemia virus type I is required for maintenance of the transformed phenotype. *Oncogene*, 7:433-7.

Yasuma K, Yasunaga J, Takemoto K, Sugata K, Mitobe Y, Takenouchi N, Nakagawa M, Suzuki Y, Matsuoka M. (2016). HTLV-1 bZIP Factor Impairs Anti-viral Immunity by Inducing Co-inhibitory Molecule, T Cell Immunoglobulin and ITIM Domain (TIGIT). *Plos Pathogens*, 12:e1005372.

Yasunaga J, Sakai T, Nosaka K, Etoh K, Tamiya S, Koga S, Mita S, Uchino M, Mitsuya H, Matsuoka M. (2001). Impaired production of naive T lymphocytes in human T-cell leukemia virus type I-infected individuals: its implications in the immunodeficient state. *Blood,* 97:3177-83.

Yoshida M, Miyoshi I, Hinuma Y. (1982). Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proceedings of the National Academy of Sciences of the United States of America* ,79:2031-5.

Yoshida M, Satou Y, Yasunaga J, Fujisawa J, Matsuoka M. (2008). Transcriptional control of spliced and unspliced human T-cell leukemia virus type 1 bZIP factor (HBZ) gene. *Journal of Virology,* 82:9359-68.

Younis I, Green PL. (2005). The human T-cell leukemia virus Rex protein. Frontiers in bioscience : *a journal and virtual library,* 10:431-45.

Younis I, Khair L, Dundr M, Lairmore MD, Franchini G, Green PL. (2004). Repression of human T-cell leukemia virus type 1 and type 2 replication by a viral mRNA-encoded posttranscriptional regulator. *Journal of Virology,* 78:11077-83.

Zhao T, Satou Y, Sugata K, Miyazato P, Green PL, Imamura T, Matsuoka M. (2011). HTLV-1 bZIP factor enhances TGF-beta signaling through p300 coactivator. *Blood,* 118:1865-76.

````
````