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Tumorigenesis and diagnostic practice applied in two oncogenic viruses: Epstein Barr virus and T-cell lymphotropic virus-1—Mini review

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ABSTRACT

To date, seven viruses have been reliably connected to various forms of human cancer: Epstein Barr Virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), high-risk Human papillomavirus (HPV), Merkel Cell Polyomavirus (MCPV), Hepatitis B virus (HBV), hepatitis C virus (HCV), and Human T-cell leukemia virus type 1 (HTLV1). This mini-review summarizes two of these viruses, EPV and HTLV-1, in terms of their general pathway of infection, the key mechanism of cancer induction, and the prominent technologies used to detect the infections. EBV is the first discovered human oncovirus and HTLV – I is the first human retrovirus and both were discovered from patient with distinct lymphoma clinical condition. Both the viruses can immortalize lymphocytes invitro and lymphomas are common manifestation of majority oncogenic viruses. Lymphomagenesis are discovered in associated with EBV, HTLV-I, Human Immunodeficiency virus (HIV), Kaposi sarcoma – associated herpes virus and hepatitis c virus. Later the undefined mechanism behind the induction of cancer by these viruses was unveiled gradually along with the responsible cofactors and mimicry mechanism. These two viruses contrast in their genetic structure, location of the infection, and latency, yet clinically, they generate similar cancer disorders. The major focus of this study is to brief the mechanism of these two unrelated viral cancer promoting agents on how they simulate a condition similar to lymphoma which may or may not undergo mimicry and cofactor utilization process, handpicked and vital genes behind the transformation mechanism are given accordingly.

1. Epstein Barr virus

The Epstein bar virus (EBV) is responsible for carcinogenesis in adult populations and is omnipresent in nature. About 90% of people are carriers of EBV as a latent infection of B-lymphocytes. EBV was first isolated as a human oncogenic virus from the cell lines of Burkitt's lymphoma in 1969 [1]. EBV is responsible for causing B lymphoproliferative disease and Hodgkin's disease, and infection may lead to Burkitt's lymphoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, and lymphomas in individuals with immunosuppression. Figs. 1–5.

EBV infection commonly occurs in younger age groups, and 80% of individuals are carriers of the infection [2–5]. EBV transmission primarily occurs via oral routes and transfusion. EBV is a human Herpes virus that belongs to the gamma sub family of herpesviruses with the *Lymphocrypto virus* genus as the prototype. EBV is generally called Human Herpes Virus 4 (HHV 4). It is a human DNA enveloped virus with a DNA-wrapped toroid-shaped protein heart, a 162-capsomer

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nucleocapsid, a protein fragment between the nucleocapsid and the envelope [6], and glycoprotein spikes in the outer envelope. EBV has a linear, double-stranded genome of about ~172 kb with DNA encoding more than 85 genes.

The open reading frame (ORF) of EBV is based on the Bam HI restriction fragment. The ORF codes for latent and lytic genes, which are subdivided into immediate early genes, early genes, and late genes. Lytic genes such as *BCRF1, BDLF2, BHRF1, BALF1,*and *BARF1* encode for human homologs [7–12]. The 17 micro-RNAs are organized into two clusters: a cluster of 10 located in the viral BART gene introns and a cluster of 3 encoded adjacent to BHRF1. Some of the latent genes remain non-translated in EBER-1 and EBER-2 [13]. Terminal repeats with a size of 0.5 kb divide the viral genome into short and long sequence domains containing coding capacity [8]. Terminal repeats serve as markers to identify EBV infection based on episome formation.

1.1. Infection mechanism

Around 90–95% of all adults globally contribute to 1.2% of EBV cancer infections around the globe [1]. These DNA viruses have toroid-shaped protein, glycoprotein spikes, and a nucleocapsid with 162 capsomers. They exhibit a characteristic clinical manifestation of acute infectious mononucleosis (Glandular fever or Pfeiffer's disease), along with classic symptoms like sore throat, fever, lymphadenopathy, and sometimes maculopapular rashes [2]. These B-cell-targeting viruses are distinctly harboured in only human hosts and persist throughout the entire reticuloendothelial system. They are transmitted via salivary droplets and predominantly infect adolescents and young adults.

CD21 and HLA class II serve as the primary receptor and co-receptor respectively for viral entry, which occurs in the B cells being that this virus targets. The primary proliferation begins in the oropharynx region upon infection of the epithelial cells [3]. This event is later extended by infecting the native B cells in the mucosal lymphoid tissue of tonsils, followed by dissemination from the latently infected memory B cells. The intermittent dissemination exposes the saliva to virus particles, resulting in active transmission to a healthy host [2].

At the lymph nodes, antigens are displayed in follicular dendritic cells of the secondary lymphoid organ's lymphoid follicles, where B cells contact antigens, resulting in incidents of normal activation of naïve B cells. These events pave the way for endocytosis of the antigen-receptor complex, antigen processing, and presenting EBV derived peptides on HLA class II molecules accordingly [4]. Activation signals are stimulated upon the migration of B cells to the edges of follicles upon contacting effector CD4 + T cells, and the B cells trespass again into the follicles and proliferate into centroblasts [4]. The isotype-switching and affinity maturation process are expected to be key factors for the maturation of B cells into either memory cells or into plasma. This process occurs as the centroblasts interact with CD4 + helper T cells [5].

The branch point event is explicitly exploited by the EBV infection mechanism. This event is the junction where cells are differentiating into memory B cells and antibody-secreting plasma cells. The virus primarily converts naïve cells into infected long-lived memory B cells via receptor-ligand interactions between centroblast B cells and CD4 + T cells [6]. The naïve B cells are transformed and immortalized by the expression of a set of latency-associated genes coding for two specific proteins, namely Latent Membrane Protein (LMP1) and Latent Membrane Protein 2 A (LMP2A). The molecular event involved in the activation of CD40 by CD40 ligand (CD154) is one important steps in stimulating B cell differentiation into plasma cells and memory cells while promoting affinity maturation and isotype switching [4].

The viral homologue of CD40 is LMP1, and the CD40-CD40L signal transduction is mimicked by LMP-1 expression, so the need for CD4 + T cell is compromised. Similarly, the B cell receptor homologue is LMP2A, which mimics the B cell receptor signalling successive copulation to

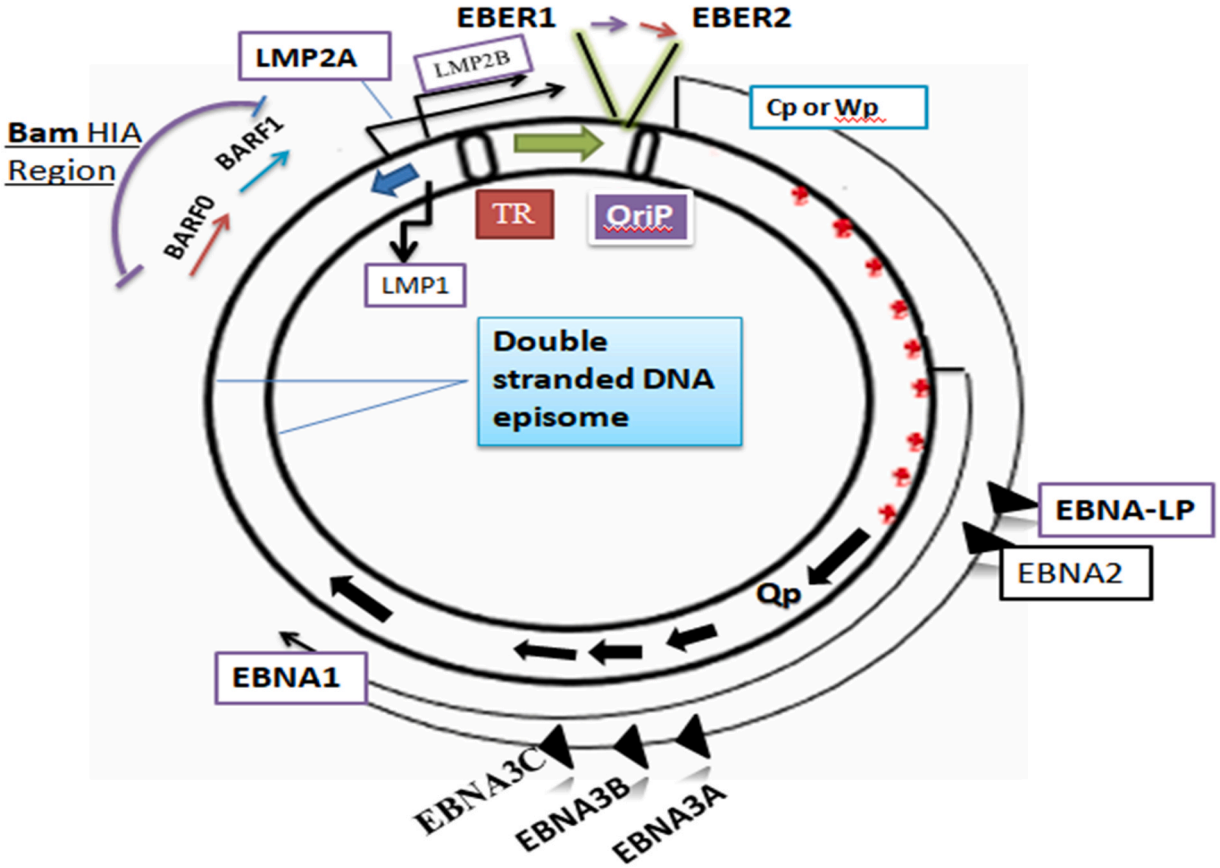

Fig. 1. Genome Structure of EBV.

LMP1 signalling promotes the affinity maturation, isotype switching, and differentiation into memory and effector B cells from parent B cells [5]. LMP1 attracts a similar cytoplasmic tail to the CD40 tail, which allows signal transduction. This process does not require ligand binding and leads to mimicking of the action of CD40-CD154 engagement originally provided by CD4 + T cells to activate B cells, and thus the subsequent differentiation into plasma cells and memory cells [4]. After differentiation and maturation, the EBV-infected B cells remain in a quiescent state with a silenced expression of the viral genome. In healthy individuals, such transformed cells remain constantly and are shed intermittently over the lifetime into the oro-pharynx region.

EBV-infected cells disseminate infectious virus particles, and the persistence of this infectious agent can be attained only upon escaping the recognition of Class I receptors with bound viral peptide activation of CD8 +cytotoxic T cells because they readily kill the infected cells [6]. Controlled expression of viral proteins helps the infected cells to escape the recognition by CD8 + T cells. Periodic lysis of infected B cells is facilitated by triggering of the B cell receptors.

1.2. Tumour induction by EBV

EBV induces cancer in immune-compromised conditions in epithelial and lymphoid locations. For unknown reasons, suppression of the lytic pathway and expression of EBV transcription programs (ETPs) lead to epithelial cell transformation into immortal and infinitely proliferating cells [7]. EBV spreads mostly via bodily fluids—saliva to be specific, and rarely, via blood and semen during sexual intercourse—as well as organ transplants, blood transfusion, and sharing objects like toothbrushes and drinking glasses. The latency protein produced by the virus is associated with the cancer mechanism [8].

EBNA-1is normally responsible for DNA replication, inhibition of MHC class I, viral genome segregation in progenies is, and enhancement of p53 degradation. This class of compounds is known to be associated with Burkitt lymphoma, Gastric cancer, and breast cancer [9]. EBNA-1 is found in association with all EBV-induced malignancies. These molecules are a specific DNA-binding protein that attaches to a highly conserved three-palindrome sequence—namely, a family of repeat elements (FR), dyad symmetry elements (DS), and sequences found downstream of the Q promoter (Qp).

EBNA-2, EBNA-3, and EBNA-LP are three latency proteins associated with post-transplant lymphoproliferative disorder [10]. They are thought to be individual compounds that have unique workload under normal circumstances. EBNA-2 aids in the upregulation of host and viral proteins and facilitates B cell immortalization. B cell immortalization is also resulted by EBNA-3, which also acts to induce transcription transactivation of both host and viral proteins. LM1/2 [8] causes a wide spectrum of clinical conditions like Hodgkin, lymphoma, breast cancer, post-transplant lymphoproliferative disorder, T/NK cell lymphoma, and nasopharyngeal cancer. Similarly these molecules tend to exhibit wide biological activity that ranges from B cell survival, upregulation of antipoptotic proteins, mimics CD40 ligand associated signaling, cell survival promoting signaling pathways and constitutively activate growth [11]. Membrane antigens (LMPs) LMP1 mimics CD40 signaling, blocks apoptosis and induces NF-kb and other cell proliferation signaling pathway. LMP2A/2B blocks BCR signaling by modulating BCR and PI3K pathways. EBNAs are classified into six categories and are expressed during the latent infection into host, which made the interpretation as these are associated with the induction of corresponding viruses. These molecules tend to exhibit many biological activities that range from B cell survival to upregulation of anti-apoptotic proteins, mimicking of CD40 ligand-associated signalling, cell survival-promoting signalling pathways, and constitutively activate growth [11].

EBNAs are classified into six categories and are expressed during the latent infection into the host, which suggest that they are associated with the induction of corresponding viruses. Immune cells are activated by excessive antigen presentation, targeting the host mRNAs involved in apoptosis, proliferation, and transformation, and micro RNAs [10]. The onset of tumour infection is anticipated to begin with the action of EBNA-1 inhibiting the antigen presentation process by MHC class I.

Cyclin D/E is a prominent factor associated with active cell proliferation regulation in this event and is activated by the interaction between EBNA-2 and EBNA-3 while EBNA-1 and EBNA-2 stimulate LMP-1 [11]. EBNA-LP activates cyclin D/E and DNA-dependent protein kinase (DNA-PKCs) directly to aid in the proliferation of cells. The later molecule interacts with anti-apoptotic protein hematopoietic cell-specific protein 1 (HS-1)-associated protein X-1 (HAX-1) [12]and promotes

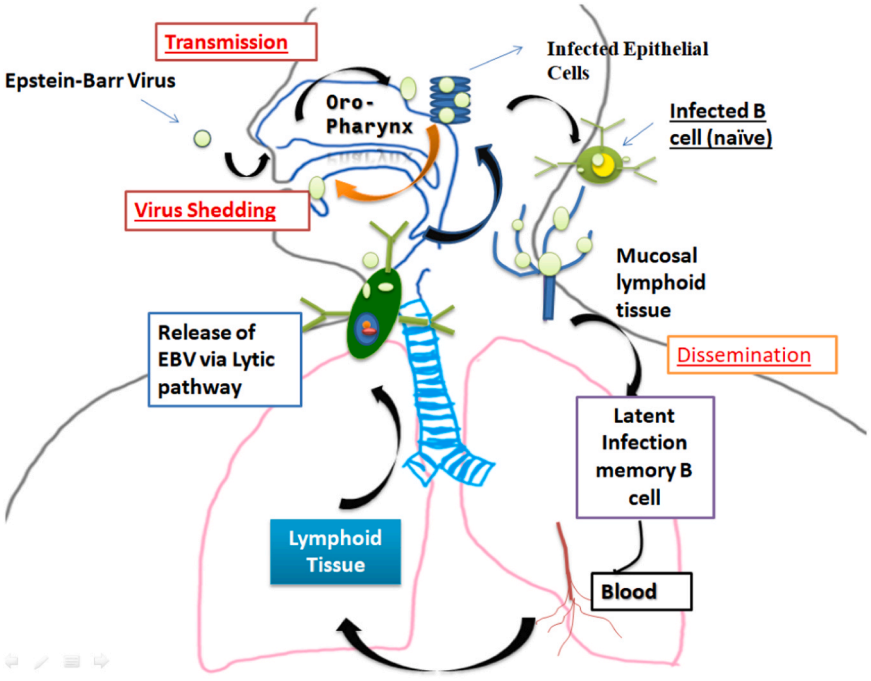

Fig. 2. Infection mechanism of Epstein-Bar Virus.

cell survival. These reactions contribute to the characteristic tumours in hosts when the virus persists in the preferred location, but the exact mechanism that contributes to the onset of the tumour is not yet discovered. Certain knowledge of the tumour is both in lymphoid and epithelial carcinoma, latent membrane protein 2 A (LMP2A)[12] at the RNA level is expressed constantly, which occurs as signalling pathways at multiple junctions that are deregulated explicitly in the cell cycle and apoptotic pathways.

1.3. Diagnostics

At any given time, around 20% of total carriers are harbouring or shedding 1–50 salivary virions per head. The EBV-infected cells either mature into memory B cells or plasma cells that are short lived. The protocol for efficient diagnosis has evolved since it was first identified in1964 using electron microscopy from a cell culture of Burkitt's lymphoma. The in situ hybridization technique [13] involves probing internally repeated *Bam*HIW11 times (in each EBV genome), but it is less fruitful to target DNA than EBV-encoded small RNAs (EBERs). Immunohistochemistry targeting LMP1, EBNA1, EBNA2, LMP2A, and BZLF1 expression corresponding to cell types from histologic lesions aids in distinguishing the latent and replicative infection [14].

The viral replicative form is identified by measuring the gene expression of BZLF1 (otherwise called ZEBRA) by immunohistochemistry. Reverse transcriptase-polymerase chain reaction (RT-PCR) and nucleic acid sequence-based amplification (NASBA) [15] are alternative methods. Although not as popular, they are recommended for accurate disease-specific results. Southern blotting techniques exploit the variable number of tandem repeats at the end of each EBV DNA molecule, where the lesional DNA primarily subjected to Bam HI restriction enzyme, followed by electrophoresis, transfer, and probing internally to detect fragments with terminal repeats [14]. This technique is used to classify band patterns into monoclonal from oligo-, poly-clonal, and uninfected tumours.

Co-amplification of EBV DNA and a control sequence spiked before DNA extraction are used in the EBV viral load assay, which is highly promising. This process is predominantly reliable in cases of immune-compromised hosts and is more sensitive, specific, and quantitative [14]. Alternative measurement can be indulging real-time measurement of PCR products. This process can reduce labour cost and is highly precise, contamination-free, and less time-consuming [16]. Sometimes, although a molecular diagnosis can be seen as a promising candidate, a copulation of traditional serological and histochemical assays along with the current molecular technique [17] can effectively work on the issue of an effective diagnosis strategy.

In the life cycle of EBV in an infected cell, three different latency patterns are known to exist [14]: Type I, Type II, and Type III latency. They are classified based on the presence of characteristic viral gene expression. EBER transcripts EBNA1 and LMP2A are expressed in Type I latency, while Type II and Type III have an additional expression. Type II expression is marked with LMP1 and LMP2B co expression, and TYPE III contains a full spectrum of latent viral gene expression, including EBNAs (1,2, 3 A, 3 C, LP), LMPs (1, 2 A, 2B), and EBER. Recognizing these expressed proteins is a major principle of all the diagnosis techniques.

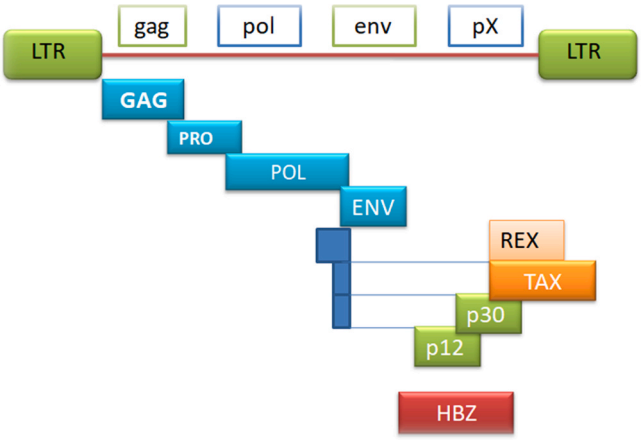

Fig. 4. Genome structure of human T-cell lymphotropic virus type-I (HTLV-1).

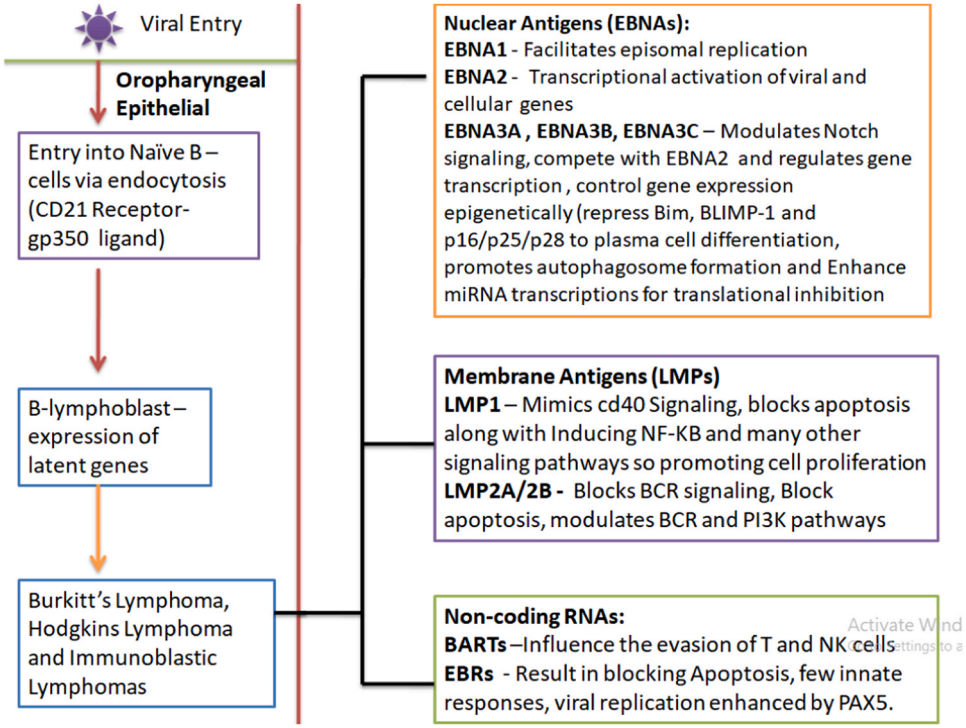

Fig. 3. Major Tumor induction factors from EBV and their role.

2. Human T-cell lymphotropic virus type-I (HTLV)

The first human retrovirus to cause a malignant tumour (leukemia or lymphoma) is Human T cell lymphotroic virus Type I (HTLV-1). HTLV-1is worldwide in distribution and was found to be endemic in the regions of the Caribbean and Southern Japan. HTLV-1is not only associated with malignant disease, but it can also cause tropical spastic parapares is, infective dermatitis, and uveitis [18]. A vaccination for HTLV-1has not been developed yet. The three major diseases caused by this virus are adult T-cell leukaemia/lymphoma, HTLV-I-associated infective dermatitis, and HTLV-I-associated uveitis.

HTLV-1is an oncovirus belonging to the Retroviridae family and is a double stranded, enveloped RNA virus belonging to Type C [19]. Being a T cell tropic (T-tropic) viruses, it causes T-cell proliferation and establishes persistent infection. The genome of HTLV-1has three structural genes (gag, pol, and env), two regulatory genes (tax and rex), and a long terminal repeat (LTR). P19 and p24 are core proteins and are encoded by the gag gene. The pol gene encodes reverse transcriptase [18]. The transmembrane protein gp21 and external envelope gp46 are encoded by the env gene. The gag gene is processed by HTLV-1protease. The expression of viral proteins and transactivation of viral replication is done by regulatory genes. Tax protein activates LTR [20].

2.1. Epidemiology and transmission

HTLV-1is found in clusters geographically worldwide. The infection is endemic in the southern parts of Japan, the Caribbean, the Middle East, South America, New Guinea, and Pacific Melanesian Islands. The sero prevalence of HTLV-1is found in higher rates in Japan at up to 30% [21]. The sero prevalence of HTLV-1is less than 10% in the United States and Europe. There is a decline in sero prevalence in populations that emigrated from endemic regions to non-endemic regions. Women are more susceptible to HTLV-1infection than men. About 50% of females above the age of 80 are infected with HTLV-I, while in the case of males, 30% are infected [22].

The most efficient mode of HTLV-1transmission is a transfusion. HTLV-1can be transmitted from mother to child during breastfeeding. Intrauterine and peripartum transmission of HTLV-1 occurs in less than 5% of children of infected mothers. Sexual transmission of HTLV-1occurs if any one of the partners is infected with HTLV-I[20]. Transfusion of contaminated blood components results in seroconversion in more than 40% of recipients. Parenteral transmission of HTLV-1occurs when drug users [23] share syringes or needles.

2.2. Cancer pathway

Formally recognized as the etiological agent of adult T-cell leukemia (ALT), HTLV-1 codes for the viral trans activator Tax protein (onco protein), which acts as a key substrate for the transformation of infected cells [24]. Pushing 1–3% of infected individuals towards risk of attracting ATL, the HTLC-produced tax protein can localize into the cytoplasm and induce wide signalling cascades, thus inducing a thrust of abrupt growth in the cell [25]. This virus can potentially escape the traditional host pathogen-recognition pathway and inhibit the immune signalling path.

Tax protein is responsible for inhibition of the TRIF-dependent TLR pathway along with the RIG-1/MDA5- dependent TLR-independent pathway. This is eventually satisfied by preventing the function of IRF7, which is responsible for transcriptional induction of innate immune genes [26]. There is a lack of studies and proper approaches in defining the onset and preferred age group of cancer induction and prevalence among all age groups, which makes making conclusions harder. Cytokines, adhesion molecules, chemokines, and chemokine receptors are expressed extensively in ATL cells [25,26].

Cell adhesion molecule 1 (CADM1) is used to identify HTLV-1-infected T cells. It is a tumour suppressor and is highly expressed in ATL cells. ATL displays up- and downregulation of certain genes.Mir-21, miR-24, and miR-146a are upregulated, whereas micro RNA miR223 is down regulated [27]. Variation and induced abnormalities in signal transduction of cell metabolism-regulating factors are the main reasons behind transformation and are mainly induced by Tax protein. These viruses do not induce tumours rapidly, and not a single mechanism leads to cell transformation. The persistent infection of the virus influences multiple mechanisms leads to tumourogenesis [28].

One of the significant steps involved in tumour induction by the HTLV-1is prolonged infection, which provokes phagocytes to release oxygen, thus altering the genes upon reaction with nitrogen radicals, proteins, and DNA [25]. Also, oncogene transfer is another prominent step in the induction of tumours. It controls the activity of tumour suppressor genes in addition to tumour induction. Another significant process done by viruses is influencing the host immune function by inhibiting it, followed by impairing of immune surveillance. All these arrays of events culminate into the clinical condition of a tumour. The invasion of a virus occurs in cells via the presence of various receptors,

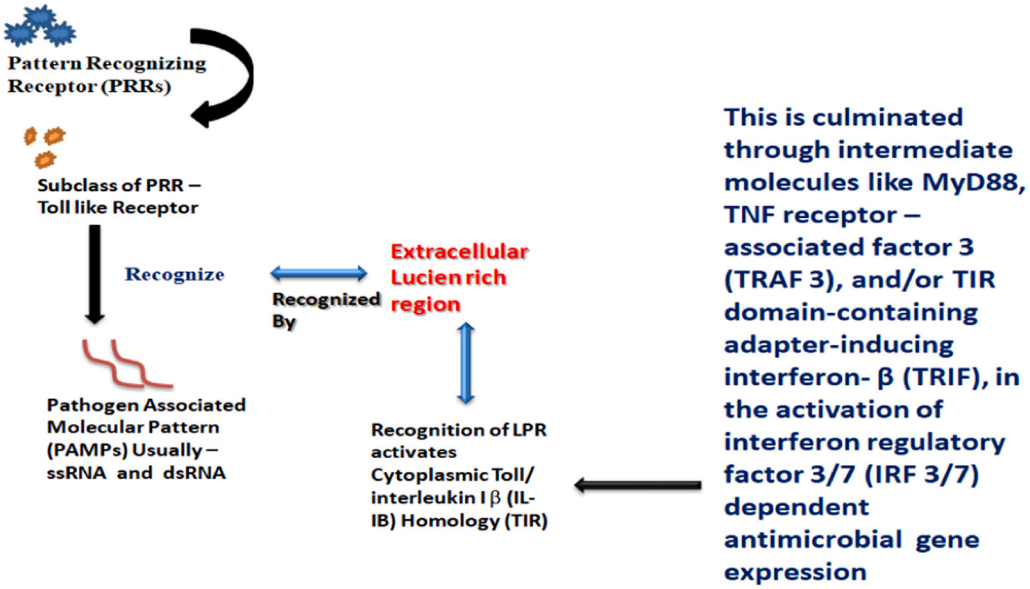

Fig. 5. Normal viral infection recognition pathway in host.

including glucose transporter (GLUT1) and heparin sulphate proteoglycan (HSPG) [29].

Viral RNA is shed in the cytoplasm upon entry of the virus into the host, and the viral entry is made possible by the interaction of HTLV-1 with HSPG and NRP-1. After the reverse transition, the viral genome transforms itself into a provirus. Telomerase induction by tax protein acts as a hallmark event in cell transformation [30]. Tax 1 is a prominent gene in tumorogenesis and is localized in the cytoplasm and nucleus. The protein suppresses nucleotide excision repair (NER) and p53, but the irony is that a high level of tax protein triggers rapid production of p53 beyond the level of requirement while impairing its function, thus resulting in the inhibition of p53-dependent NER. Tax 1-mediated activation of NF-kB deregulates autophagy [31–33].

HBZ is a leucine zipper factor present in the minus strand of HTLV-1. It is also the least immunogenic as anti-HBZ antibodies have yet to be discovered and are an important factor in the regulation of cell proliferation and immune escape [32]. HBZ suppresses a pro-apoptotic gene, Bim, which is controlled by a transcription factor named FoxO3a. The role of HBZ in to bind with FoxO3a and de-arm its apoptotic process. The presence of this protein specifically aids in cell proliferation by interacting with enhancer binding protein α (C/EBP α). C/EBP α deregulates cancer cell proliferation by binding with HBZ, which removes the barrier for proliferation [34]. The overall role of HBZ is preventing the apoptosis and autophagy of the infected cells.

An additional path that ensures the complete restriction of autophagy is the inactivation of mTOR [32]. Overall, the onset of transformation of a cell upon infection into a cancer cell is a cooperative event that occurs due to alteration in metabolism by a virus upon persistent infection and influencing the area of infection with multiple genetic modifications. This leads to the acquisition of characteristics like escaping the host immune responses, immortality, continuous proliferation, and silencing viral proliferation. Cytotoxic T lymphocyte (CTL) response against Tax gene expression will eliminate expressing cells after expression of host immunity over HTLV-1, where clonal expansion as alternative form of replication that is initiated due to commence of anti-HTLV-1 immunity, in this course of event the virus replicates as provirus to ensure longevity. Low immunogenicity of HBZ promotes the survival of HBZ expressing cell at immediate life cycle process immediately after proviral replication of Tax encoded cells. This opens up to fact that HTLV-1 initially expand as de novo promoted by tax following this after establishment of host immune response to HTLV-1, the viral count elevates by clonal expansion of infected cell due to expression of HBZ [32,33].

2.3. Detection and vaccine

Serological screening of HTLV-1antibodies in infected patient samples were done by an enzyme immunoassay (EIA) or particle agglutination test [34,35]. Viral lysate in first-generation EIA resulted in false-positive results. Second-generation EIA is performed using synthetic HTLV-1or recombinant proteins of HTLV-1peptides, which eliminates false-positive results [36]. Confirmatory tests are still required to eliminate false-positive results and to detect the type of HTLV infections. Several other serological based tests such as Indirect immunofluorescence assay(IFA) (screening test), Western blot (confirmatory test) and line immunoassays(confirmatory test) are available. The drawback of these confirmation tests is that they cannot differentiate HTLV-1and HTLV-2 infections, and indeterminate results may occur when samples react with one or more antigens in the test but they lack typical HTLV profile (i.e., reactivity to gag or env gene is not seen)[34].

Apart from serological tests, several generic or HTLV-type specific PCR methods were developed. Proviral HTLV-1DNA is amplified in PCR and real-time PCR. A load of provirus is expressed as the number of HTLV-1DNA copies per fixed number of mononuclear cells in peripheral blood. It is frequently used as a marker for prognosis and disease progression in infected patients [35–37]. The reduction of HTLV-1infection is possible by counselling infected patients about sexual and breast-feeding practices. Preventive immunization is the best method to decrease the rate of HTLV-1infection [35,38]. A Therapeutic vaccine is a feasible way to prevent infection by carriers of HTLV-1infection. Synthetic peptides and recombinant proteins for characterizing immune dominant epitopes of HTLV-1are used. A universally immunogenic vaccine has to be developed using animal models [39].

3. Conclusion

These two genetically unrelated cancer inducers have unique pathways to cause cancers, although they express a common character of promoting cell transformation upon persistent infection, escaping the host immune recognition, and stopping the cell from being killed after the duration, the mechanism followed is unique. The mode of transmission marks the primary difference and is thus a direct factor for determining the location of virus infection. EBV is extensively studied, and almost every aspect of cancer induced by EBV is elucidated. Hence, data on EBV invasion, infection, and transformation is available, but there is a lack of proper studies on the HTLV-1 virus in the aspects of transformation and the mechanisms of persistent infection.

For both the viruses, no common mechanism of tumorigenesis has been witnessed, and both have multiple processes to transform cells. EBV employs multiple genes to regulate the lifetime of cells and is more complex than HTLV with respect to stimulated metabolism to make a cell immortal. HTLV is an RNA virus that employs a specific gene set that interferes with the entire transformation process.

CRediT authorship contribution statement

Arun Chandra Manivannan: Conceptualization. **Vinitha Devaraju:** Conceptualization. **Palanivel Velmurugan:** Writing – original draft. **Thangavelu Sathiamoorthi:** Writing – original draft. **Subpiramaniyam Sivakumar:** Writing – review & editing. **Arumugam Veera Ravi:** Supervision.

Coonflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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