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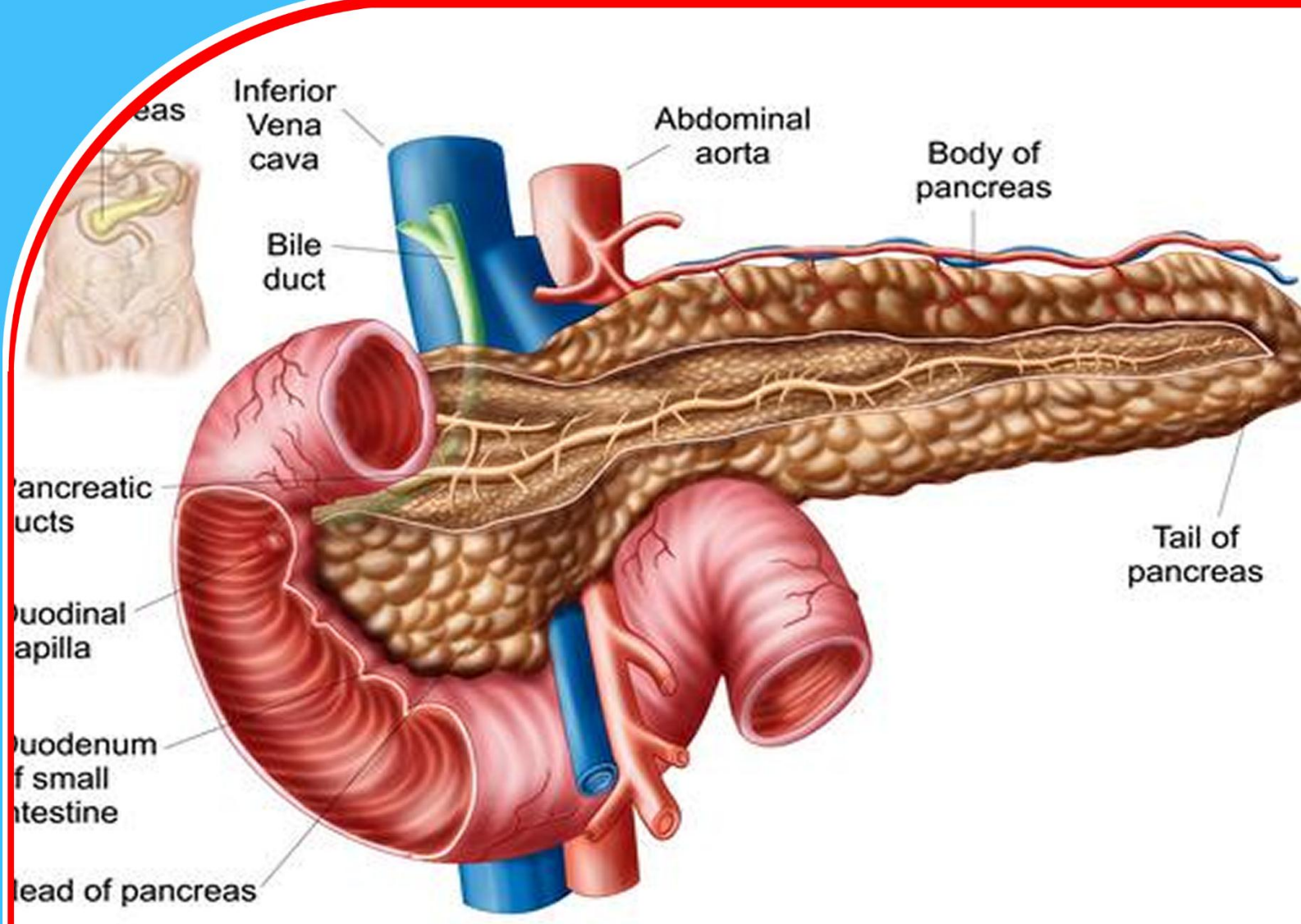

Human T-cell lymphotropic virus type 1 oncogenesis and cell-to-cell spread

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ABSTRACT

Exploring host-HTLV-1 interactions and the molecular processes underpinning HTLV-1-mediated carcinogenesis is crucial for establishing effective treatments for viral infection and associated leukemia/lymphoma. Several HTLV-1 proteins have been shown to play important roles in the cellular transformation and immortalization of infected T cells. Through interactions with MAVS, STING, and RIP1, the HTLV-1 oncoprotein Tax suppresses the innate IFN response, resulting in the inhibition of TBK1-mediated phosphorylation of IRF3/IRF7. The HTLV-1 protein HBZ affects genomic integrity and inhibits target cell death and autophagy. Furthermore, it has been discovered that HBZ promotes the growth of ATL cells and aids in the evasion of infected cells from immunosurveillance. It currently appears that the efficacy of an individual's cytotoxic T cell (CTL) response to HTLV-1 is the most important single predictor of that person's provirus load, which can differ by more than 10,000-fold amongst HTLV-1-infected persons. We examine recent improvements in our knowledge of the pathophysiology, or underlying processes, of the illness produced by HTLV-1 infection in this article. Furthermore, we explore the future approach for targeting HTLV-1-associated malignancies and anti-HTLV-1 therapies. The pathogenic agent of adult T-cell leukemia/lymphoma (ATL) is human T-cell lymphotropic virus type 1 (HTLV-1). ATL is a fast-developing clonal tumour of CD4+ T cells which are cellular and viral protein interactions and pave the way for the discovery of new classes of cellular modulators, which may induce Tax oncogenesis and its impact on survival signalling pathways such as the NF-B and PI3K-Akt pathways, therapeutic target opportunities for ATL have been presented in two collaborative studies.

Keywords: *Human T-cell lymphotropic virus type 1, Adult T-cell leukemia/lymphoma, HBZ, Tumorigenesis, innate immunity, Tax.*

Introduction

The human T-lymphotropic virus type 1 (HTLV-1) is linked to two forms of disease: adult T cell leukemia/lymphoma (ATL) and a variety of chronic inflammatory illnesses. HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is the most well-known chronic inflammatory illness, in which lesions in the central nervous system (CNS) produce progressive weakening, stiffness, and paralysis of the legs. Human T-cell leukemia viruses (HTLVs) are complex retroviruses that belong to the primate T-lymphotropic virus (PTLV) family [1]. The Delta-retroviruses genera of the Orthoretrovirinae subfamily contain HTLVs [2]. Simian T-lymphotropic viruses (STLVs) were passed from monkeys to humans in Africa around 30 000- 40 000 years ago and ultimately developed into HTLVs. Since then, HTLVs have spread to many geographic locations as a result of human migration [3]. Nonetheless, STLVs with strong similarity to HTLVs are still present in Africa [4]. Four varieties of HTLVs have been discovered, namely HTLV1/2/3/4. The first carcinogenic HTLV in humans, HTLV-1, was found in the early 1980s by two distinct research groups in the United States and Japan [2, 5]. The virus primarily infects T cells and has a positive single-stranded RNA genome [6]. It is estimated that around 10 million people worldwide are infected with HTLV-1, yet the majority of them remain asymptomatic for the remainder of their lives [7]. Only a tiny percentage of HTLV 1-infected people (2–5%) develop adult T-cell leukemia/lymphoma (ATL), an extremely severe type of leukemia [7]. HAM/TSP (HTLV-associated myelopathy/tropical spastic paraparesis), a kind of neurological demyelinating illness, is another significant HTLV-1-associated condition [8,9]. Furthermore, three further HTLV genotypes, HTLV-2, HTLV-3, and HTLV-4, have been discovered and characterized [10]. HTLV-1 and HTLV-2 infections are more common than HTLV-3 and HTLV-4[11]. Although the CD4+ T-cell are the main target cells of HTLV-1, many other types of cells, such as CD8+ T-cell, endothelial cells, B-lymphocytes, myeloid cells, and fibroblasts, can also be infected with HTLV-1[12, 13].

The immune response to HTLV-1

HTLV-1 usually induces a significant immunological response. The serum antibody titer corresponds with the HTLV-1 provirus load and can surpass. However, it is unclear whether this high antibody titer contributes significantly to HTLV-1-associated illness prevention or pathogenesis, or to managing the equilibrium provirus load. The ability of HTLV-1 to travel directly from cell to cell, without the requirement for wrapped extracellular virions [14]. It implies that HTLV-1 has been subjected to a small amount of selection pressure from antibodies. Env protein, on the other hand, is expressed on the surface of naturally infected lymphocytes [14]. At a low level, anti-Env antibodies may impair the effectiveness of HTLV-1 cell-to-cell transmission.

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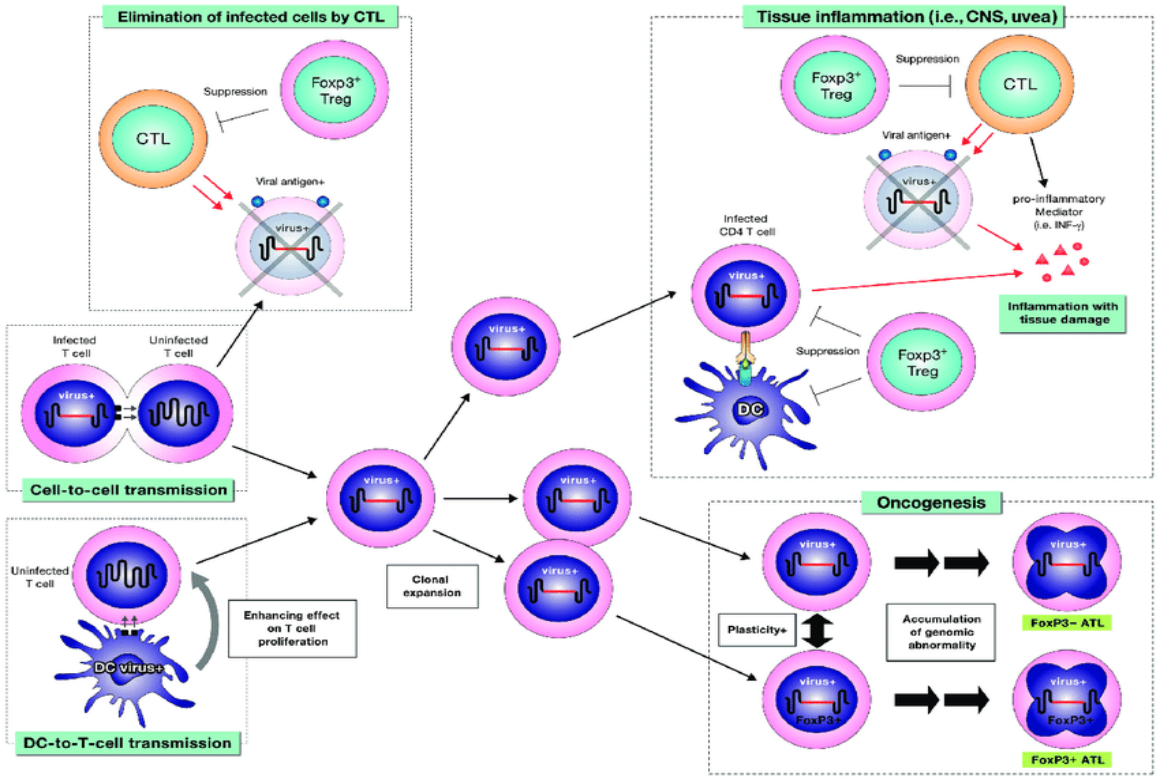

Figure 1: HTLV-1 infection in the host immune system. HTLV-1 enters and dysregulates the host immune system, resulting in chronic inflammation or transformation of infected cells

The helper T cell response

The CD4+ T cell response to HTLV-1 has been challenging to examine since HTLV-1 infection of a CD4+ T cell – HTLV-1's major host cell – immediately stimulates activation and proliferation of the cell, as well as production of several host genes, including IFN-c. These events rule out typical antigen-specific CD4+ T cell tests that rely on antigen-induced cellular proliferation or cytokine generation. Using a short-term ELISPOT technique to avoid this issue [15], researchers discovered that the median frequency of HTLV-1-specific CD4+ T cells was 25 times higher in patients with HAM/TSP than in asymptomatic HTLV-1 carriers with a similar provirus burden. Th1-type cells predominated among HTLV-1-specific helper T cells in both HAM/TSP patients and asymptomatic carriers. The high frequency of HTLV-1- specific CD4+ T cells is consistent with the hypothesis that such cells, activated by contact with HTLV-1 antigens in vivo or by infection of the cell itself by HTLV-1, cause the inflammatory lesions that result in tissue damage in the associated diseases such as HAM/TSP. The dominant HTLV-1 antigen recognized by CD4+ T cells was Env protein [15]. Interestingly, there was evidence of preferential HTLV-1 infection of these virus-specific CD4+ T cells: although most of the provirus was present in cells of other specificities, HTLV-1 was detected consistently at a higher frequency in HTLV-1-specific CD4+ T cells than in human cytomegalovirus-specific CD4+ T cells [15]. The CD8+ T cell response to HTLV-1 was first detected by Kannagi and her colleagues [16], who made the interesting observation that HTLV-1-infected cells become susceptible to CD8+ T cell-mediated lysis before

the appearance of detectable Env protein on the cell surface. This observation presaged the discovery that cytotoxic T cells (CTL) recognize peptides derived from processed cytoplasmic proteins [17]. The main features of this unusual CD8+ T cell response [18], are the high frequency of HTLV-1- specific CD8+ T cells and their state of chronic activation. In most virus infections, CD8+ T cells play a critical role in limiting virus replication, by killing virus-infected cells and by secreting IFN-c. It was therefore natural to propose [19], that HTLV-1-specific CD8+ T cells played a major part in determining the provirus load at equilibrium, and that individual variation in provirus load was caused by individual variation in the efficiency of this response.

Genotypes of HTLVs

Four genotypes of HTLVs have been found as described above. HTLV-1 can be transmitted via body fluids, e.g., blood, breast milk and semen [20]. Transmission from mother to child occurs primarily via breast-feeding and rarely through transplacental or intrapartum transmission in endemic regions [21,22]. In most cases, sexual transmission occurs from a man to a woman during sexual intercourse [20,21,22]. Moreover, human-to-human parallel transmission, primate-to-human transmission, and non- human transmission have also been observed [23]. Previous studies have sought to determine the mechanism underlying the oncogenesis of HTLV-1. It has been shown that HTLV-1, unlike other acute transforming retroviruses, is neither able to induce tumors rapidly nor able to upregulate the expression of cellular proto-oncogenes [24]. In general, viral infections can initiate and promote tumorigenesis by any of the following mechanisms: induction of chronic inflammation in the host, suppression of the host immune defense, insertional mutation in the host genome and activation of virally carried oncogenes that mediate cellular transformation [20,21,22]. First, a prolonged and persistent infection with HTLV-1 results in chronic inflammation in the host. Then, phagocytes release reactive oxygen species at the inflammatory site, which interact with nitrogen radicals, causing damage to the cell membrane, DNA and proteins and altering the gene expression profiles and enzymatic activities.

Consequently, these responses induce carcinogenesis and enhance neoplasia [25]. Second, HTLV-1 infection can cause the insertion of efficient oncogenes into the host genome, which reduce the expression of tumor suppressor genes or directly stimulate mitosis of the host cells [26]. Third, HTLV-1 infection can also inhibit the host immune function and impair immune surveillance, and thus, pre-cancerous cells can escape from host immunity [26]. However, novel insights into the precise mechanisms by which HTLV-1 induces tumorigenesis are expected to be discovered in the future using new approaches. Importantly, it is thought that HTLV-1 infection happens early in life and has a long latency period before cancer appears. Thus, the vast majority of effort has focused on the prevention of HTLV-1-mediated tumorigenesis. Because the exposure to HTLV-1 in early life plays an important role in cancer development later in life, it is practical to develop interventions targeting early life exposure to the infection [27]. HTLV-2 was initially described in 1982[28]. Molecular biology experiments have defined four major subtypes of HTLV-2, namely, HTLV-2A/B/C/D [29]. HTLV-2 is relatively less pathogenic than HTLV-1. HTLV-2 infection ends in sub-acute neurological syndromes, such as neuropathies and paraparesis, despite being very rare [30,31]. Human HTLV-3 and HTLV-4 are two new members of the HTLV family. Although a number of distinguishing characteristics of HTLV-3 and HTLV-4 have been revealed, the pathogenic potential of these human retroviruses remains to be determined. Both HTLV-1 and HIV-1 target cells of the immune system, particularly CD4+ T-cell, and cause them to grow abnormally (HTLV-1).

Biological structure of HTLVs and their components

Similar to other retroviruses, HTLV-1 begins its life cycle by targeting specific cells. HTLV-1 contains an RNA genome in the virion [32]. Upon viral entry, the viral RNA is reverse transcribed into a double-stranded DNA, which can be integrated into the DNA genome of the host cell, resulting in the provirus [33]. HTLV-1 has a relatively small (9 kb) genome, but it can express multiple products by utilizing various strategies, including polycistronic translation, frame shifting, alternative mRNA splicing, and protease-mediated cleavage of large viral proteins into smaller polypeptides with specific functions [34].

HTLV-1 and HTLV-2 have common molecular features and exhibit approximately 70% nucleotide sequence homology [35]. HTLV-3 has approximately 62% nucleotide sequence homology with HTLV-1, and HTLV-4 shares approximately 62%– 71% sequence identity with HTLV-1, HTLV-2, and HTLV-3[36]. However, there is one major difference between the nucleotide sequences of HTLV-1/2 and HTLV-3/4: the long terminal repeats (LTRs) of HTLV-3/4 lack the distal 21-bp transcription regulatory repeat sequences, i.e., Tax-responsive elements (TREs), and possess only two 21-bp repeat sequences, while the LTRs of HTLV-1/2 have three of these 21-bp repeat sequences [36,37]. In addition to the two LTR-containing cis-acting regulatory sequences of the provirus, all four HTLV genotypes contain the structural genes gag, pro, pol, and env and the regulatory genes tax and rex [38]. HTLV-1 encodes four different auxiliary proteins, including p13, p30, p12 and p8. These proteins play crucial roles during HTLV-1 infection. p30 decreases the expression of Tax, a viral transcription trans activator, thus promoting viral latency and persistence and helping the virus escape from immune surveillance [39].

Similar to p30, p13 also enables the virus to bypass immune surveillance by increasing the production of mitochondrial ROS (reactive oxygen species) [40]. As a result, p13 may promote viral latency and persistence [41]. The p12 inhibits the activation of cytotoxic T lymphocytes (CTLs) and natural killer cells (NK), hence protecting the virus against immune surveillance. p8, a proteolytic cleavage product of p12, accelerates T-cell contact by augmenting the number and length of cellular conduits among T-cell and enhances the envelope-dependent transmission of HTLV-1[42]. The figure shows Endosomal recognition of HTLV-1 viral RNA by TLR7 leads to MyD88-dependent signalling. IRAK4, IRAK2 and TRAF6 activate the kinase complex (NEMO/IKKa, IKKb) driving classical NF-kB activation. TLR7 signalling also activates IRAK4, IRAK1 and TRAF6 leading to the activation of IRF7. These signalling pathways are further manipulated by HTLV-1 viral proteins Tax and HBZ. Tax expression can constitutively activate the NF-kB pathway by cytoplasmic binding of NEMO and nuclear interaction with CBP; Tax has also been shown to inhibit the RIG-I-MAVS-TBK1 pathway that leads to antiviral signalling. Conversely, nuclear expression of HBZ inhibits the NF-kB signalling by repressing p65-dependent transcription.

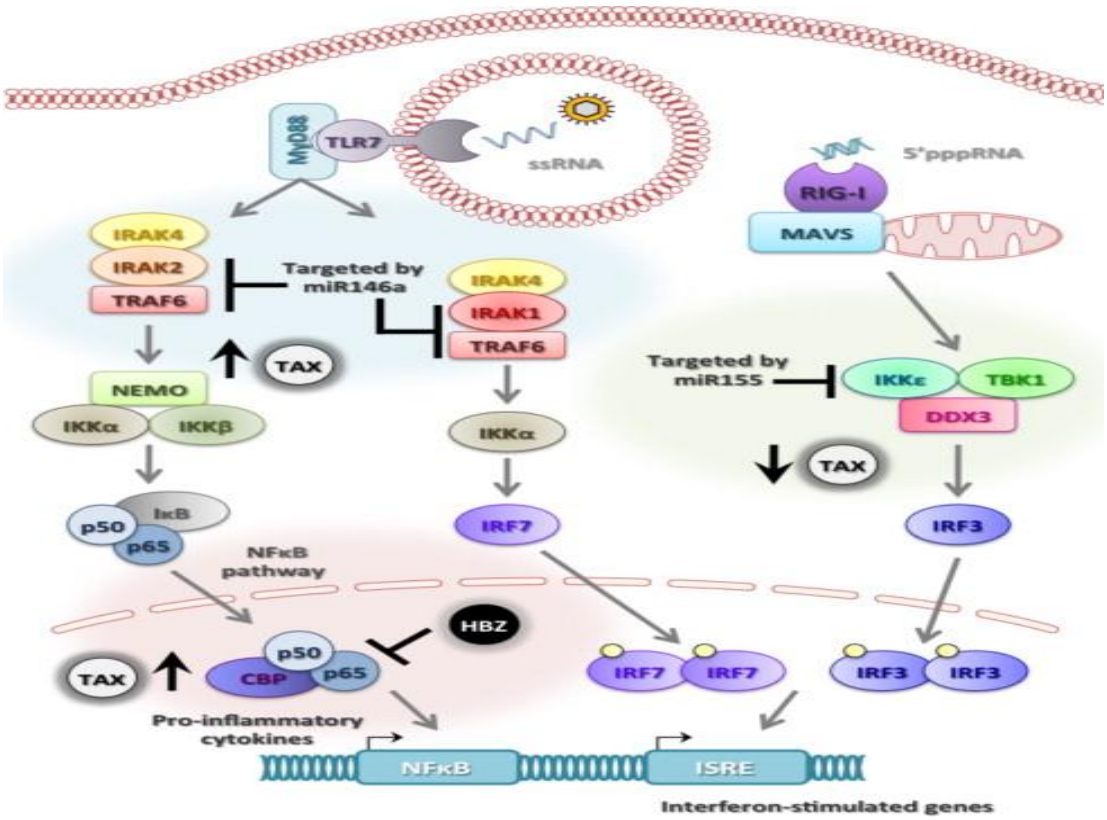

Figure 2: Positive and negative regulation of IRF and NF-kB pathways by HTLV-1

Roles of HTLV-1 genes in tumorigenesis

HTLV-1 is etiologically linked to adult T-cell leukemia/ lymphoma (ATL) [43]. The genetic structure and regulation of HTLV-1 are more complex than those of other leukemia viruses [44]. In addition to the structural genes (gag, pro, pol, and env) encoding the characteristic virion proteins, the genome of HTLV-1 also carries genes that encode the nonstructural proteins, Tax and HBZ, which are needed for regulating viral gene expression. Although considerable progress has been made in understanding the intricate mechanism of ATL caused by HTLV-1, further investigation is required to elucidate the function and regulation of the viral gene products and their interactions with one another, as well as with cellular factors. Tax of HTLV-1 plays an essential role in cellular transformation and interaction with the host innate immune system Early studies have shown that Tax-1 is predominantly localized in the nucleus and accumulates specifically in the speckled structures of the nucleus [45,46]. Recently, it has been reported that Tax-1 is also localized in the cytoplasm [47,48,49], although the mechanism regulating the subcellular localization of Tax-1 remains to be elucidated. The N-terminal region of Tax-1 contains a CREB-binding region [50], which is required for its interaction with proteins involved in cell cycle progression, transcription and cell signaling regulation [51,52]. As a viral oncoprotein, Tax-1 plays a critical role in tumorigenesis and contributes to the pathogenesis of ATL by regulating several intracellular signaling pathways, including IκB kinase (IKK)/NF-κB signaling pathway [53], DNA damage repair pathway, and the innate immune signaling pathways, such as RIG-I/MDA5-dependent and TLR-independent pathways, TRIF-dependent TLR pathways and the recently discovered cGAS-STING pathway [54,55]. Tumor cells are typically characterized by

genetic and phenotypic instability, referred to as the mutant phenotype [56]. Due to internal (metabolic) and external (genotoxic stress) factors as well as errors in DNA replication, genomic injuries can occur [57]. Typically, these errors are corrected immediately by numerous cellular repair mechanisms [57].

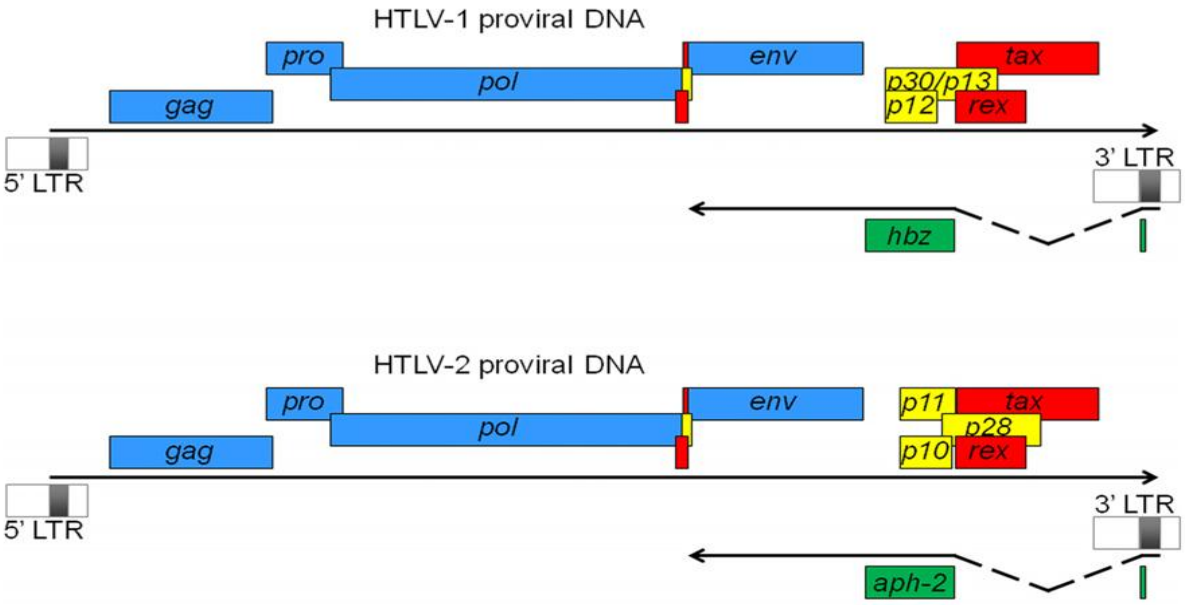

Figure 3: Comparison of HTLV-1 and HTLV-2DNA and genes

If these repair pathways cannot be tightly coordinated, the genomic lesions may develop into mutations during cell division and DNA replication, thereby leading to genomic instability. It is thought that a prominent feature of HTLV-1 transformed cells is the genomic instability that is caused by Tax-1-mediated inhibition of the cellular DNA repair pathways [58] and increased mutations in the cellular genome [57]. The random nature of these mutations indicates that this viral protein could directly and indirectly interfere with the DNA damage repair pathways, including BER (base excision repair), NER (nucleotide excision repair), MMR (mismatch repair), NHEJ (non-homologues end joining) and HR (homologous recombination). In particular, Tax-1 has been demonstrated to suppress the NER pathway through the transactivation of PCNA (proliferating cell nuclear antigen), a cofactor for DNA polymerase δ that plays a crucial role in DNA replication and repair [59,60]. In addition, by the inactivation of p53, Tax-1 can interfere with the function of the tumor suppressor [61]. Tax-1 directly targets the beclin1- containing autophagy molecular complex to deregulate autophagy by stimulating the IKK complex, resulting in the persistent activation of NF-κB [62]. Autophagy not only has significant roles in preventing inflammation and viral infections but also suppresses tumorigenesis by maintaining chromosomal integrity [63].

Conclusion

In spontaneous infection, HTLV-1 is constantly transcribed. At equilibrium, however, complete cycle replication contributes just a little net contribution to HTLV-1 replication. The true ratio of mitotic replication (as a provirus) to infectious replication (through reverse transcriptase) is difficult to calculate. Individual heterogeneity in the effectiveness of the CTL response to the virus

is one of the most important single elements that accounts for the difference between people in the equilibrium provirus load in healthy HTLV-1 carriers. Strong mRNA expression of granzymes and other CTL lysis-related genes, as well as fast killing of HTLV-1-infected cells, define an effective CTL response associated with a low provirus burden. At equilibrium, the frequency of CD8+ T cells specific to a persistent replicating pathogen is not a reliable indicator of the efficiency of that CD8+ T cell response. Recently, viral proteins Tax and Rex of HTLV-1 have attracted a large amount of attention in clinical medicine. Based on their sequence homology, all Tax proteins possess a CBP/p300 binding region. These functional domains show some differences among Tax-1, Tax-2, Tax-3 and Tax-4.

One of the major differences is related to the lysine residue at position 85 of Tax-1. Further investigations of host factors altered in ATL may be helpful in identifying potential targets for effective therapies against this type of leukemia. Moreover, investigations on the subcellular localization of Tax proteins will provide useful information for addressing the mechanisms underlying the interaction of Tax with host factors. It has been shown that Tax oncoproteins perturb IFN production and signaling in HTLV-1-infected cells, and a better understanding of the molecular basis of this process would allow us to develop strategies to counteract Tax and re-establish the innate IFN response against the viral infection. In addition to Tax proteins, Rex plays an important role in HTLV pathogenesis. Further studies are still required to define its precise function. HTLV-1 infection, a neglected and life-long disease, is currently still incurable and untreatable. The prevention of infection-associated cancers might be able to reduce a substantial proportion of human cancers. To prevent the spread of HTLV-1, a safe and effective vaccine is required.

Recommendation

The study of virus-host interaction leads to a better understanding of the molecular processes of viral protein and host cellular response in the pathogenesis of infection or virus spread. In the case of HTLV-I, such cellular and viral protein interactions pave the way for the discovery of new classes of cellular modulators, which may induce Tax oncogenesis and its impact on survival signalling pathways such as the NF-B and PI3K-Akt pathways, therapeutic target opportunities for ATL have been presented in two collaborative studies. Furthermore, a new therapy strategy is being developed in our group for HAM/TSP patients based on the results of an IFN- research and epigenetic investigations.

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