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Review article

Molecular biology of human T cell leukemia virus

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ABSTRACT

Human T cell leukemia virus type 1 (HTLV-1) is a horizontally transmitted virus infection of CD4+ lymphocytes which causes adult T cell leukemia-lymphoma (ATLL) and HTLV-associated myelopathy (HAM). The viral genome encodes two oncoproteins, transactivator protein (Tax) and helix basic zipper protein (HBZ), which are considered tumor initiator and maintenance factors, respectively. Tax is the primary inducer of clonal infected T cell expansion, and genetic instability. The immune response to Tax results in the selection of cells with little or no Tax expression, which have undergone genetic and epigenetic alterations that promote T cell activation, proliferation, and resistance to apoptosis. This selection of malignant cells occurs over several decades in 5% of infected individuals. Novel insights into the molecular details of each of these events has led to targeted therapies for ATLL.

Introduction

Human T-cell leukemia viruses (HTLV) are members of the δ-retrovirus genus, which are exogenous horizontally transmitted viruses found in several groups of mammals.[1] The δ-retrovirus members include HTLV and simian T-cell leukemia virus (STLV) strains 1–4, and bovine leukemia virus (BLV). HTLV-1 has infected 5–20 million individuals, based on various estimates, with the highest endemic rates of infection in southern Japan, the Caribbean islands, Central and South America, parts of Africa, northeast Iran, and Australian and Melanesian aborigines.[2] HTLV-2 is found in native North, Central, and South Americans, and in parts of Africa.[3] In the United States, the HTLV-1/2 seroprevalence rate among volunteer blood donors averages 0.016%.[4] HTLV-3 and 4 have been isolated in a small number of bush-meat hunters in Cameroon.[5]

HTLV-1 is the most clinically significant HTLV member. Approximately 5% of HTLV-1 infected individuals develop clinical disease.[6] These disorders include a rapidly progressive, therapy refractory, and fatal form of T-cell lymphoproliferation, characterized as leukemia or lymphoma, and designated adult T cell leukemia (ATL) or adult T-cell leukemia-lymphoma (ATLL). In addition, HTLV-1 causes a debilitating myelopathy (HAM), as well as uveitis, infectious dermatitis, and other inflammatory disorders (including pneumonitis, arthritis, myositis). HTLV-2 has been associated with milder neurological disorders and chronic pulmonary disorders, although the etiological relationship remains controversial.[7] HTLV-3 and 4 are not associated with a clinical disorder.[8]

Several excellent reviews of HTLV-1 molecular biology have been published.[9,10] The current review highlights recent ideas regarding the molecular basis of ATLL.

Viral genome

The HTLV-1 genome is 8.5 kilobases (kb) in length (Fig. 1).[11,12] The genome is a plus, single-stranded RNA with a 5′cap and a 3′poly-A tail. Two copies of the viral genome are packaged in each virus particle. The viral RNA is reverse transcribed in infected cells into double stranded (ds) DNA, which is integrated almost randomly in the genome of the infected cell. The integrated DNA includes long-terminal repeats of approximately 600 bp, which regulate initiation and termination of viral RNA synthesis.

The viral genome includes classical retroviral genes found in avian and other mammalian retroviruses, *gag, protease (pr), pol,* and *env.* The Gag (Group-Specific Antigen) protein is synthesized as a 55 kd precursor protein, that is processed by the viral protease into a matrix protein (MA) of 19 kd, a capsid protein (CA) of 24 kd, and a nucleocapsid (NC) protein of 15 kd. MA is situated at the inner surface of the viral lipid membrane. CA is the major structural component of the viral nucleocapsid. NC binds the viral genome and promotes reverse transcription. Pr is an aspartyl protease that processes the Gag, Gag-Pr, and Gag-Pr-Pol precursor proteins. Gag-Pr and Gag-Pr-Pol are synthesized from the same viral RNA that encodes Gag, but are the result of ribosome frameshifting events during translation. The Pol protein includes the 62 kd viral polymerase, reverse transcriptase, and the 32 kd viral integrase.

The Env glycoprotein is synthesized as a 66 kd precursor protein, which is processed by cellular furins in the endoplasmic reticulum (ER) into a 45 kd surface Env protein (SU) and a 21 kd transmembrane Env protein (TM). The Env proteins form a trimer on the surface of the virus particle. The SU protein binds to the virus receptor, and subsequent conformational changes of the SU-TM complex lead to fusion of the virus membrane with the target cell membrane.

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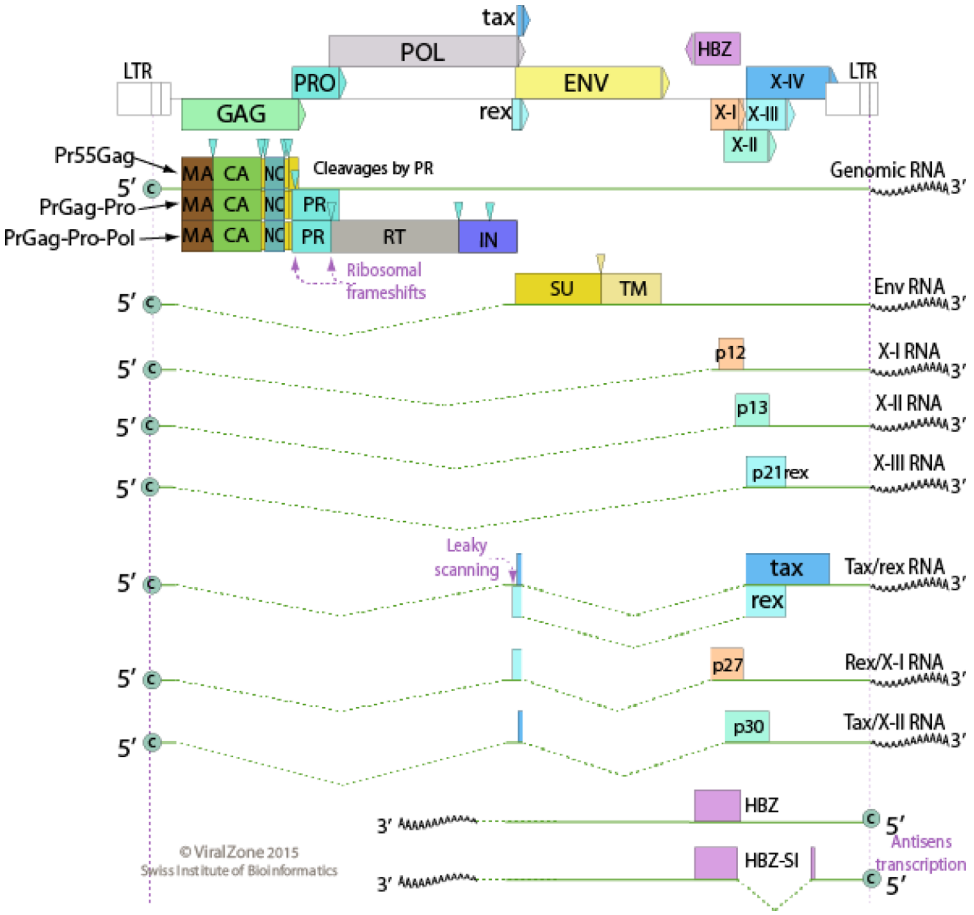

Fig. 1. HTLV-1 genome. The integrated provirus utilizes the promoter in the 5′LTR to drive transcription. This results in an unspliced full length mRNA that serves as genomic RNA to be packaged into virions. It is also used as a template for translation of Gag, Gag-Pr (1 ribosomal frameshift), and Gag-Pr-Pol (2 ribosomal frameshifts) polyproteins. The single spliced mRNA encodes Env that is cleaved into SU and TM envelope proteins. Completely spliced mRNAs encode Tax and Rex. Four accessory protein, p27I, p12I, p13II, and p30II are produced by alternative splicing of ORFs I and II. The p8I protein is a proteolytic cleavage product from p12I. The HBZ proteins are produced from unspliced and spliced mRNAs encoded by minus strand transcripts. Reprinted with permission from Viral Zone.[58]

Unlike classical mouse and avian retroviruses, δ-retrovirus genomes encode additional non-structural non-enzymatic proteins that regulate replication and pathogenesis. Tax (transcriptional activator protein from the X-gene region) is a 40 kd protein that potently promotes viral transcription via interaction with CREB-binding protein (CBP) and p300 to promote the activity of the cAMP-response protein (CREB) – activated T cell factor (ATF) transcription factors.[13] Tax promotes cellular transcription via interaction with activators of the serum-response factor (SRF) that act through Fos and other immediate early proteins. Tax also promotes cellular transcription via binding to the regulatory (γ) subunit of the IκB (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor) kinase complex, resulting in activation of the nuclear factor kappa B (NFκB) transcriptional pathway. In addition, Tax binds several proteins resulting in repression of cell cycle inhibitors, checkpoint proteins, and DNA repair proteins. Together, the Tax-binding and Tax transcriptional target proteins have been designated the “Tax interactome”.

Rex is a 30 kd protein that regulates nuclear export of viral RNA.[14] This occurs through interaction with a stem-loop structure, known as the Rex-response element (RRE), present in the 3′ non-coding sequences of all viral plus strand RNAs. The HTLV-1 p12 and p8 ORF I proteins are ER and Golgi proteins which promote NFAT (nuclear factor of activated T cells)-induced T cell activation.[15] The p8 protein also promotes cell adhesion and virus transmission via cellular conduits.[16] The p30 ORF II protein is a nuclear transcription factor that represses CBP/p300 activity.[17] The p13 ORF II protein is a mitochondrial protein that promotes the generation of reactive oxygen species and T cell activation.[18] The 45 kd HBZ (helix basic zipper) protein is expressed from a gene on the viral antisense or minus strand. It binds to several different proteins involved in viral activation and cellular signaling.[19]

Replication and transmission

HTLV-1 binds to a wide range of human cell types through interactions with heparin sulfate proteoglycans, glucose transporter I, and neuropilin-1.[20] The mechanism of viral entry as well as early steps in virus uncoating remain poorly defined. HTLV-1 is capable of infecting a wide range of human cells *in vitro*, but in infected patients, the majority of virus infected cells are CD4+ lymphocytes. Reverse transcription occurs in the cytoplasm, and the complex of viral dsDNA is imported into the nucleus with the integrase. The linear viral dsDNA is integrated into the cellular genome at many sites with a preference for transcription start sites with a bias towards transcription factor binding sites, particularly those utilized by STAT1 (signal transducer and activator of transcription 1), TP53 (tumor protein 53), and HDAC6 (histone deacetylase 6).[21] The integrated viral DNA (provirus) may be latent, with no active plus strand transcription, or it may be actively transcribed.[22] Unspliced, single spliced, and multiple spliced viral RNAs are exported from the nucleus for translation. The unspliced viral RNA is also utilized for viral genomic RNA packaging. Virus assembly occurs at the plasma membrane with the precursor Gag, Gag-Pr, Gag-Pr-Pol proteins, and the SU and TM Env proteins.[23] The resultant virus particles detach from the plasma membrane, the viral protease is autocatalytically processed, and then it promotes cleavages of the precursor structural proteins. This results in an infectious virus particle that is transmitted to target host cells, primarily by cell-to-cell contact rather than as cell-free virus particles.[16] Cell-to-cell transmission involves a viral synapse, analogous to the immunological synapse that occurs in antigen presentation to T cells. However, dendritic cells can also be infected by cell-free virus.

Cells have evolved a broad range of restriction factors that inhibit

replication of different retroviruses. The cytidine deaminase, APOBEC 3 G, has been shown to restrict HTLV-1, inducing hypermutation in the viral genome.[24] HTLV-1 is also restricted by the exonuclease and deoxynucleotide triphosphohydrolase SAMHD1 (SAM domain and HD domain-containing protein 1) which depletes deoxynucleoside triphosphates required for reverse transcription.[25] However, HTLV-1 can circumvent SAMHD1-dependent restriction, although the way this occurs is not understood. It remains to be determined whether other restriction factors or immune sensors also regulate HTLV-1 infection.

Oncogenesis

HTLV-1 is an oncogenic virus in culture and infected patients. Recent information explains why infection is often prolonged over many decades prior to the development of malignancy, and in only about 5% of infected individuals.[26] The current model is that infected cells expand within an infected individual primarily through cellular division of already infected cells rather than virus release and infection of new host cells.[10] This process has been designated clonal expansion. The two viral oncoproteins, Tax and HBZ, are thought to be critically involved in the clonal expansion process. This process is characterized by genetic instability with the accumulation of multiple genomic and epigenomic alterations. Key secondary alterations are hypothesized to be important in the development of ATLL.

Tax

Tax expression is considered to be a key early driver of both virus expression and lymphoproliferation. Tax activation of transcriptional factors NFκB, SRF, and CREB, results in transcriptional activation of cytokines and their receptors, and inhibition of apoptosis.[13] Tax repression of p18 and DNA polymerase β results in abnormal cell cycle regulation, and suppresses DNA repair. Tax functional inactivation of p16, p53, mitotic arrest deficient protein 1 (MAD1), and transforming growth factor β signaling promotes abnormal cell cycle regulation, genetic instability, and inhibition of apoptosis. TAX binds to numerous PDZ proteins, which result in activation of the phosphatidyl inositol 3 kinase (PI3K)-Akt pathway.[27]

However, Tax is also a highly immunogenic protein.[28] Thus, immune evasion mechanisms down-regulate Tax expression, through several different mechanisms. Promoter hypermethylation occurs in the 5′LTR, inhibiting *tax* expression.[29] Tax recruits several inhibitors of proviral transcription, including STK11 (serine threonine kinase 11), SIRT1 (nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-1), TCF7 (transcription factor 7), and LEF1 (lymphoid enhancer binding factor 1).[30–32] In some cases, deletions and inactivating mutations are found in the 5′LTR and *tax* coding region in the HTLV-1 genome in ATLL cells. Recent work has demonstrated dynamic expression of Tax in some cases of ATL, within a small proportion of ATL cells at a given time, which promote survival of the entire population of cells through an indirect mechanism that remains to be deciphered. The strong cytotoxic T cell (CTL) response directed against Tax selects for T cells with low or no Tax expression.

HBZ

The *hbz* gene is continuously expressed in all HTLV-1 infected subjects thoughout infection, and it is only weakly immunogenic. It has weak transforming activity, independent of Tax, and it has been proposed to be a tumor maintenance factor. The *hbz* RNAs include spliced and unspliced forms that promote T cell proliferation, independent of their coding capacity. The HBZ protein binds a wide range of proteins including those involved in signaling pathways, such as Smad 2,3, (Mothers against decapentaplegic homologs 2,3), NFAT, MafB (musculoaponeurotic fibrosarcoma oncogene homolog B), CREB/ATF and Jun family proteins, FoxO3a (forkhead box transcription factor 03a), IRF-1 (interferon regulatory factor 1), CBP/p300, p65 (NFκB subunit p65 or RelA), TCF1, LEF1, CENP-B (centromere protein B), T cell phenotype (FoxP3, forkhead box protein 3)), and DNA repair (GADD34, growth arrest and DNA damage protein 34). Thus, HBZ inhibits apoptosis, autophagy, inflammation, and disrupts genomic integrity. HBZ counteracts many of the functions of Tax, thus maintaining a persistent latent infection.

Genetic alterations in ATLL

Genomic analysis of ATLL cases identified a high rate of mutations (2.9/Mb), particularly within the Tax interactome.[33] Mutations were particularly common in genes responsible for T cell receptor-NFκB signaling, T cell trafficking, and T cell-related pathways, as well as immunosurveillance (Fig. 2). Activating mutations were identified in PLCG1 (phospholipase γ1), PRKCB (protein kinase c β), CARD11 (caspase recruitment domain-containing protein 11), VAV1 (Vav guanine nucleotide exchange factor 1), IRF4, FYN (59-kDa member of the Src family of kinases). CCR4 (chemokine receptor 4), and CCR7. Gene fusions were also notable, including CTLA4-CD28 (cytotoxic T-lymphocyte-associated protein 4 – cluster of differentiation protein 28 required for T cell activation) and ICOS-CD28 (inducible T-cell costimulator precursor – CD28). Intragenic deletions were noted in IKZF2 (zinc finger protein Helios), CARD11, and TP73, as well as mutations in

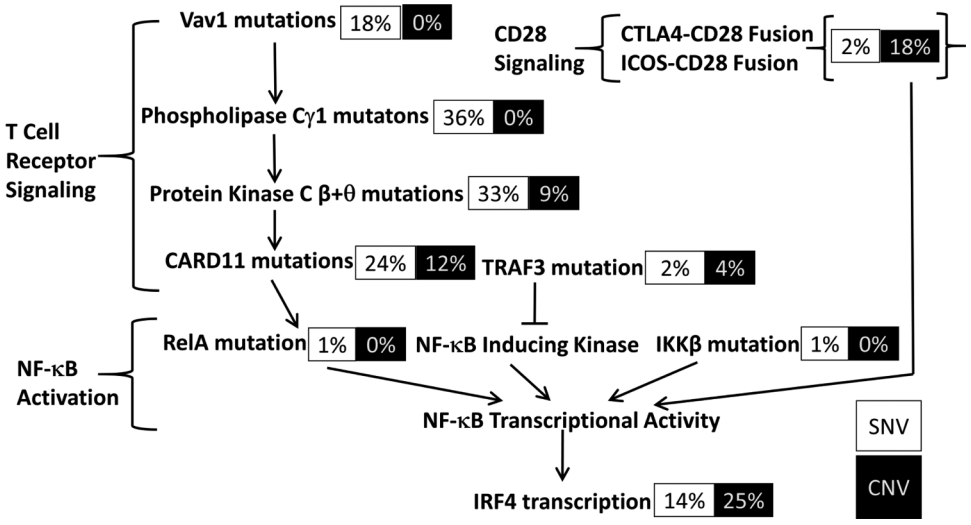

Fig. 2. TCR Activation Pathway in ATLL. The figure depicts percentage of cases in which eachin the pathways is mutated in ATLL. SNVs are depicted in black font, CNVs in white font. Reprinted with permission from reference.[50] This research was originally published in Journal of Biological Chemistry. (c) the American Society for Biochemistry and Molecular Biology.

GATA3 (GATA-binding protein 3), HNRNPA2B1 (heterogeneous nuclear riboprotein A2/B1), GPR183 (G-protein couple receptor 183), CSNK2A1 (casein kinase II subunit 2 alpha 1), CSNK2B, and CSNK1A1. These findings suggest that HTLV-1 infected cells develop mutations in these key oncogenic pathways survive and proliferate despite immunological selection for low levels of Tax expression.

Epigenetic alterations in ATLL

Oncoproteins of human tumor viruses regularly interact with the cellular epigenetic machinery.[34] Tax activates expression of the genes for arginine and histone methyltransferases, and silences histone deacetylase 1 (HDAC1) gene expression. Epigenetic regulatory proteins, including histone deacetylase inhibitors and DNA methylation inhibitors have been shown to reactivate the latent HTLV-1 provirus.[22] In contrast, bromodomain and extra-terminal (BET) protein inhibition suppresses Tax-mediated tumorigenesis by inhibiting NFκB signaling.[35]

Key epigenetic alterations also occur in ATLL, when Tax is no longer expressed. Immortalized, but untransformed cells display very similar epigenetic changes as those in transformed ATL cells, suggesting that epigenetic changes are likely an early event in leukemogenesis. ATL is characterized by prominent CpG island DNA methylation, leading to transcriptional silencing.[36] These alterations occur without mutation at TET2 (Tet Methylcytosine Dioxygenase 2, IDH2 (isocitrate dehydrogenase 2), and DNMT3A (DNA methyl transferase 3A). Aberrant activation of EZH2 (protein coding enhancer of Zeste 2 polycomb repressive Complex 2 subunit), has been described in ATL, resulting in trimethylation of histone H3 lysine (K) 27, and suppression of a wide range of different genes.

A binding site (BS) for the epigenetic barrier element, CTCF, has been identified in the integrated HTLV-1 provirus.[37] Portions of the genome upstream of the CTCF-BS are extensively methylated at CpG sites, and bound histone 3 proteins are modified by K36 trimetylation. In contrast, portions of the genome downstream of the CTCF-BS are generally unmethylated at CpG sites, and bound histone 3 proteins are marked by K4 trimethylation. Moreover, chromatin loops between the CTCF-BS in the provirus and adjacent cellular CTCF-BS result in transcriptional activation of cellular sequences.[38] These findings suggest that the quarternary structure of the infected cell DNA may be a determinant of leukemogenesis.

Model for ATLL development

The current view of HTLV-1 transformation describes a multi-step process. Initial steps of infection may occur in dendritic cells, which then present virus to mature T cells or their precursors, via cell-to-cell transmission of the virus (Fig. 3). The number of infected cells expands as a result of virus replication, and clonal amplification of infected cells. The growth promoting effects of HTLV-1 are largely attributed to the effects of the Tax protein. Tax also promotes genetic instability, leading to genetic and epigenetic alterations within infected cells. The level of Tax is regulated by HBZ, and the host immune response targets Tax, and Tax-induced viral gene products. Thus, infected cells evade these responses by down-modulating Tax expression. However, intermittent and transient expression of Tax by small numbers of cells within the infected cell population continue to drive T cell expansion and genetic damage. Thus, there is likely considerable genetic heterogeneity in the infected cell population. There is selective expansion of infected cells that have undergone cellular alterations that promote cell proliferation, resistance to apoptosis, and evasion of the immune response. Subpopulations of infected cells with key genetic and epigenetic changes evolve into leukemia or lymphoma. The prolonged period of evolution of the malignancy likely also contributes to therapy resistance, since effective anti-tumor treatments cooperate with active tumor immunity.

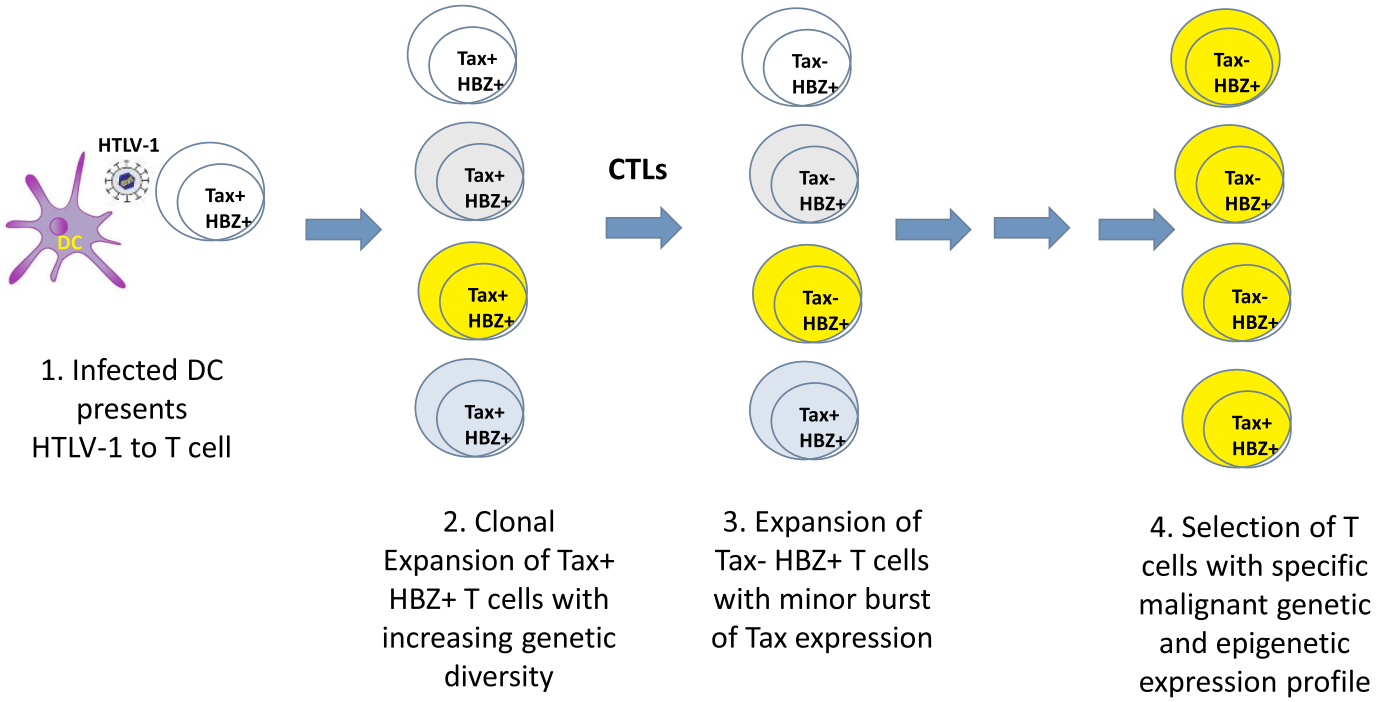

Fig. 3. Multiple events of HTLV-1 infection and transformation. The schematic hypothesizes that the initial HTLV-1 infected cell is a dendritic cell which presents infectious virus to a T cell. Subsequent expression of Tax, HBZ, and plus strand virus genes result in infection and clonal expansion of other T cells, resulting in genetic heterogeneity, as indicated by different colored cells. Immune responses, as well as viral gene restrictions, result in little or no Tax and plus strand gene product expression from the majority of infected T cells, but a minor population of T cells with transient bursts of Tax expression. Several decades of infection result in selection of cells with specific combinations of genetic and epigenetic alterations that result in adult T-cell leukemia lymphoma.

Implications for ATLL therapy

Therapies that block HTLV-1 replication include nucleoside reverse transcriptase inhibitors (e.g. zidovudine, abacavir) and integrase inhibitors (e.g. raltegravir). Protease inhibitors and non-nucleoside reverse transcriptase inhibitors developed for HIV-1 have little activity against analogous proteins of HTLV-1. Antivirals may impact viral load only during early stages of infection or during transient bursts of virus replication, but do not inhibit clonal expansion of previously infected cells. Thus, their role in HTLV-1 infected individuals remains unclear.

The combination of zidovudine (ZDV) and interferon alpha (FIN) has significant activity in chronic and acute forms of ATLL, but not in the lymphoma subtype of ATLL. It is doubtful that this combination is functioning by inhibiting virus replication, but more likely has direct cytotoxic effects on the cells.[39] Zidovudine inhibits tolemerase and reactivation of p53 during cellular senescence.[40] Arsenic trioxide (AsO3) synergizes with IFN to induce cell cycle arrest and apoptosis of ATLL cells. This combination induces proteasomal degradation of Tax, with shutoff of the NFκB signaling pathway.[41] Clinical trials of the combination of ZDV, IFN, and AsO3 for ATLL have been initiated.[42]

Several therapeutic efforts have focused on Tax or Tax-induced gene products. A therapeutic vaccine directed at Tax was tested in a clinical trial of ATLL, resulting in remission in two of three treated subjects.[43] Moreover, several Tax-induced proteins have been targeted for ATLL therapy. The α subunit of the interleukin 2 receptor (CD25) is highly expressed on ATLL cells.[44] Thus, antibodies and radioimmunoconjugates directed at CD25 have shown activity in ATLL treatment.[45] Another Tax-induced protein is chemokine receptor CCR4, which is over-expressed on ATLL cells.[46] A monoclonal antibody to CCR4, mogamulizumab, is an effective agent in refractory ATLL or in combination with chemotherapy or ZDV/IFN.[47]

Activating mutations in the TCR signaling pathway may also be targets for ATLL therapy.[33] Protein kinase c (PKC) is activated by mutation in its gene or that for upstream mediator, phospholipase γ. Several inhibitors have been developed and tested in clinical trials. Enzastaurin is a highly specific PKC β inhibitor which was well tolerated in previous trials in subjects with B cell lymphomas.[48] Midostaurin is a multikinase inhibitor, approved for FLT3-mutated acute myelogenous leukemia, which has significant activity against PKC β.[49] Studies of these agents against ATLL cell lines are reasonable.

Another member of the TCR pathway is interferon regulatory factor 4 (IRF4). This gene is mutated in 33% of ATLL cases, and over-expressed as a result of upstream mutations in the majority of ATLL cases.[50] Levels of IRF4 in ATLL have been shown to correlate with prognosis.[51] Direct inhibitors are currently being evaluated in other diseases in which IRF4 has been shown to be pathogenic, including multiple myeloma.[52] Another approach to inhibit IRF4 expression is the use of an immune modulatory imide drug (IMID), such as lenalidomide.[53] Lenalidomide binds to the E3 ubiquitin ligase, cereblon, and increases its activity.[54] This promotes ubiquitination and degradation of transcription factors Ikaros and Aiolos, and overcome their ability to promote IRF4 synthesis.

A downstream transcriptional target of the TCR pathway are members of the Myc protein family, Inhibitors of the BET family have been shown to repress Myc expression, and possess activity against ATLL cells in culture.[55] Currently, BET inhibitors are under investigation in other clinical settings.[56]

Aberrant epigenetic changes in ATLL may also be therapeutically targeted. EZH2 inhibition was shown to reverse polycomb-dependent alterations in ATLL and selectively eliminate leukemia and HTLV-1 infected cells in culture.[57]

Conclusions

Insights into the molecular biology of HTLV-1 are leading to the development of targeted agents for ATLL. It is expected that these studies may provide an effective approach to this almost uniformly fatal malignancy, as well as approaches for prognostication and prevention of this disorder.

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