Viewpoint

Is the human T-cell lymphotropic virus type 2 in the process of endogenization into the human genome?

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ABSTRACT

Human T-cell lymphotropic virus type 2 (HTLV-2) infection has been shown to be endemic among intravenous drug users in parts of North America, Europe and Southeast Asia and in a number of Amerindian populations. Despite a 65% genetic similarity and common host humoral response, the human T-cell lymphotropic viruses type 1 (HTLV-1) and 2 display different mechanisms of host interaction and capacity for disease development. While HTLV-1 pathogenicity is well documented, HTLV-2 etiology in human disease is not clearly established. From an evolutionary point of view, its introduction and integration into the germ cell chromosome of host species could be considered as the final stage of parasitism and evasion from host immunity. The extraordinary abundance of endogenous viral sequences in all vertebrate species genomes, including the hominid family, provides evidence of this invasion. Some of these gene sequences still retain viral characteristics and the ability to replicate and hence are potentially able to elicit responses from the innate and adaptive host immunity, which could result in beneficial or pathogenic effects. Taken together, this data may indicate that HTLV-2 is more likely to progress towards endogenization as has happened to the human endogenous retroviruses millions of years ago. Thus, this intimate association (HTLV-2/human genome) may provide protection from the immune system with better adaptation and low pathogenicity.

Introduction

Human T-cell lymphotropic viruses, encompassing the human T-cell lymphotropic virus type 1 and 2 (HTLV-1 and HTLV-2), which make up, with the Simian T-cell lymphotropic virus (STLV), the primate T cell-lymphotropic viruses (PTLV), are members of the delta-retrovirus genus.[1] Primate retrovirus cross-species jumps have occurred for hundreds or thousands of years.[2] Continuous interspecies transmission between a non-human and human primate species with overlapping natural habitats is probably the origin of seven HTLV-1 subtypes (A to G) a few thousand years ago.[3,4] Fig. 1 describes a retrovirus phylogenetic inference extracted from the Gypsy Database (GyDB)[5] which shows evolutionary evidence of several viral transmission events between primates, and even between distant species, that have occurred in the past.

Phylogenetic divergence between HTLV-1 and HTLV-2 has occurred more than one million years ago but they still share about 65% of nucleic acid sequences.[6,7] Therefore, despite a significant similarity

they have distinct pathogenic properties. HTLV-1 was the first human retrovirus discovered and has mainly been associated with two illnesses, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATL).[8–11] On the contrary, HTLV-2 is described as an asymptomatic or minimally infectious agent[12] with just punctual clinical cases reported.[13]

HTLV-1 and HTLV-2 have distinct oncogenic properties.[14,15] They primarily integrate their genomes into T cells, leading them to immortalization.[16] HTLV-1 preferentially infects $CD4^+$ T cells while HTLV-2 $CD8^+$ T cells, even though both viruses are detectable in these two populations.[17] Unlike HTLV-1, which is able to induce an aggressive malignant proliferation of activated $CD4^+$ T cells, such as in ATL,[18] HTLV-2 promotes an oligoclonal proliferation of non-malignant $CD8^+$ T cells.[14]

Estimates of the global number of HTLV-1 and HTLV-2 infected individuals range from 10 to 20 million.[19] Some countries in Africa, the Caribbean basin, South America and Japan are considered to be areas of higher endemicity.[19] HTLV-2 infection has been shown to be endemic among intravenous drug users in parts of North America, Eu-
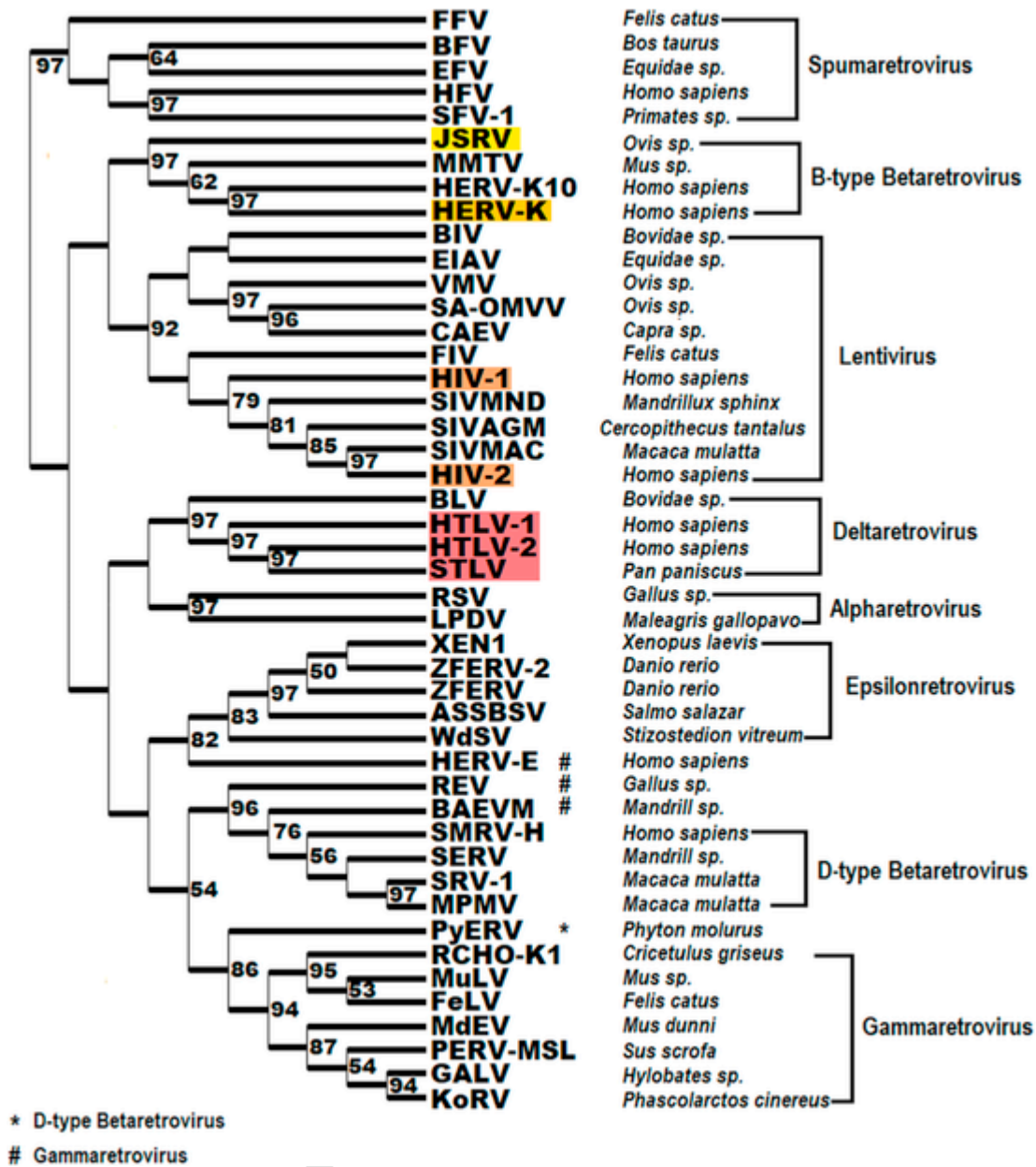
Fig. 1. Evolutionary evidence of transmission events between primates and distant species in the past. Note: Phylogenetic inference extracted from Gypsy Database (GyDB).

rope and Southeast Asia[20,21] and in a number of Amerindian populations.[22–25] Some indigenous communities, such as the Kayapo, who inhabit the Amazonian basin, have a 47% prevalence of infection.[24] Their ancestors most probably came to the Americas through the land bridge, the Bering strait, connecting Asia to the Americas, up to some twelve thousand years ago.[26] Given the high prevalence of infection in Japan, it is interesting to speculate whether the virus had come to the Americas from Asia with those ancient immigrants. Despite the high HTLV-2 incidence, clinically symptomatic patients are not in large numbers.

Benign or low pathogenic HTLV-2 infection may be related to viral latency provided by accessory proteins.[14] While, HTLV-1 accessory proteins are an important driving force for infectivity, cell proliferation and transformation, the pathogenic impact of HTLV-2 accessory proteins is attenuated.[14] Despite Tax-1 and Tax-2 homology, differences in activity may be responsible for the outcome of the infection.[27] Tax-1, unlike Tax-2, causes DNA damage, activates the non-canonical NF-κ

B pathway and deregulates autophagy.[14,27–29] HTLV-1 HBZ and HTLV-2 APH-2 viral proteins play a similar role, but with subtle differences resulting in low HTLV-2 pathogenicity. Unlike APH-2, HBZ is a more stable protein and can repress IRF-1, a component of innate immunity, and enhance TGF-beta signaling and subsequent Foxp3 expression, thereby inducing a $CD4^+$ regulatory T cell phenotype.[30]

Additionally, we note that HTLV-2 infection induces a decrease in beta-chemokine production[31] and seems to be more adapted to the human host which may provide an enhanced type of immune responses during HIV-1 co-infection as compared to HIV-1 infection alone with delayed progression to AIDS.[32,33] Furthermore, HTLV-2 as mediated by Tax2 expression can down-regulate CCR5 expression on lymphocytes, thereby modulating HIV-1 infection and replication.[34]

As well as the HIV-1/HTLV-2 co-infection relationship, some endogenous retroviruses (ERVs) play a critical role in protecting the host against infection from related pathogenic and exogenous retroviruses.[35] For example, an endogenous version of the Jaagsiekte sheep retro-

virus (enJSRV) interferes with the replication of exogenous JSRV, acting like a restriction host mechanism.[36] Furthermore, enJSRV-26, a specific provirus which was integrated in the host genome recently, exerts an antagonistic effect on exogenous beta-retroviruses in sheep.[36] Surprisingly, enJSRV-26 endogenization occurred around 200 years ago after sheep domestication.[35,36]

In the human host, HIV-1 infectivity and core assembly are altered due to the interference of Gag formation by HERV-K Gag particles.[37] HIV elite controllers present HERV-K Gag specific cellular and humoral responses that promote an immunoprotective effect.[38,39] Biological processes that can be favorable to the host are an important requirement for retroviral endogenization. Thus, some ERV proteins play a role in host defenses against retroviral infection. In summary, the protective ability of endogenous retroviruses against infection by related pathogenic retroviruses seems to be an important driving force that positively selected and fixed endogenous retroviruses.[35]

When considering that a "candidate" for viral endogenization should have some degree of adaptation such as a low pathogenic course in exogenous retrovíruses, HTLV-2 could be in this process. HTLV-2 has been infecting human beings since the Prehistoric Period and a minority of individuals have presented with an illness. There is obviously an advantage for a virus to have the ability to escape immune selection. However, the HTLV-2 envelope protein becomes non-functional with only a limited number of mutations, which is in contrast to the HIV-1 envelope.[40] The mutation rate is lower in HTLV-2 than in HIV-1, conferred by accurate reverse transcription.[41] Moreover, HTLV-2 uses the host DNA polymerase during clonal expansion of infected cells as a replication strategy, which decreases mutation rates and contributes to viral genomic stability.[42] Compared to endogenous retroviruses, exogenous retroviruses such as HIV-1 and HTLV HTLV-2 have a higher replication rate, embedded into the host genome. A decreasing trend in retroviral replication rate is observed in more recently emerging retroviruses when compared to older ones[43] (see Table 1). Mutation rates are also much lower among ERVs than exogenous retroviruses, since the former are subject to the lower evolutionary rates of the host genome,[3] in contrast to exogenous retroviruses where the reverse transcription step is not subject to editing or error correction.[44]

Viral endogenization has resulted in a massive insertion of endogenous viral elements from diverse origins and ages which are distributed in the human genome and other vertebrates.[48,49] Retrovirus endogenization seems to be occurring after continuous retroviral invasion and integration in the germ cell genome.[35,50] The HTLV-2 integration locus in T cells is variable, with no specific chromosomal integration site or pattern identified within transformants.[51]

The integration process in the host germ cell genome is also required for the endogenization process. Despite the fact that the HTLV-2 genome has not been found integrated into the germinal cells,[45,46] we can speculate about the possibility of its integration into the germ cell chromosomes. A good example among human retroviruses is HIV-1 which appears to integrate in the male cell genome. HIV-1 DNA was detected in sperm after chromatin decondensation, suggesting a viral presence in the sperm nucleus or integration into its genome.[45] In addition, HIV-1 particles in sperm cells from AIDS patients can be transferred to normal oocytes.[46] Despite the absence of a CD4$^+$ T cell membrane receptor in sperm cells, HIV-1 can use a galactosylceramide-like compound as an alternative receptor.[46,47] Therefore, due to the molecular plasticity of retrovíruses, it is not surprising that HTLV-2 was able to find a receptor to infect germ cells.

From an evolutionary point of view, the exogenous genome integration into the germ cell chromosome of host species could be considered as the final stage of parasitism and evasion from host immunity. The extraordinary abundance of endogenous viral sequences in the genome (more than 8%) of all vertebrate species, including the hominid family, is evidence for this invasion.[52] As expected, evolutionary competition between endogenous and exogenous retroviruses is a continuous balancing process, the potentially pathogenic effects of endogenous viral elements to the host being compensated by its beneficial effects.[52]

Taken together, this data may indicate that HTLV-2, regardless of subtypes, is on its way towards potential endogenization, as shown by the example of an exogenous Koala retrovírus, known for its role in the etiology of neoplasia, that has endogenize in some koala populations.[53] This process may have happened to HERVs millions of years ago.[44] However, pathogenicity is related to cell specificity and not cytotoxicity. A good example is the rabies virus which is hardly cytotoxic but leads to cell death. In contrast, enteroviruses are highly cytotoxic with a rapid turnover but allow patients to recover. One may suggest that if a virus infects the germline, its original pathogenicity may be relevant providing infected people have enough time to reproduce, which would be the case for HTLV-2.[54] Thus, this intimate association (HTLV-2/human genome) provides potential protection from the immune system and some adaptive properties from retrovíruses such as HTLV-2. This hypothesis suggests that HTLV-2 represents a possible example of ongoing in vivo endogenization.

Table 1

Characteristics of human retroviruses and human diploid cells.

Variable	HIV-1	HTLV-1	HTLV-2	HERV	Human diploid cells
Mutation rate	10^{-4}	10^{-5}	10^{-6}	10^{-6}	10^{-7}
Viral load (no treatment)	High	Low	Very low	Absence	Absence
CD4$^+$ T cells loss	Yes	No	No	No	—
CD8$^+$ T cells increase	Yes	Yes?	Yes?	No data	—
IL-2 production	decreased	Increased	Very high?	No data	—
Estimated time in human genome (years)	$\sim 10^2$	10^6	10^7	10^8	10^9
Apoptosis rate	High	Low	Low	Very low	Very low
Morbidity (no treatment)	High	Intermediate	None	None	0

HERV: human endogenous retroviruses; HIV-1 human immunodeficiency virus type 1. HTLV-1: Human T-cell lymphotropic virus type 1; HTLV-2: Human T-lymphotropic virus type II; IL-2: interleukin-2-.
Note: HTLV-3 and HTLV-4 were not included for lack of data.

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