HYPOTHESIS

Human T-Lymphotropic Viruses Evolution Possibly Explained by Primate Deltaretrovirus Geographical Segregation

Luis Isamu Barros Kanzaki1 and Jorge Casseb2

1Laboratory of Molecular Pharmacology, Faculty of Health Sciences, University of Brasilia, Darcy Ribeiro University Campus, Brasilia, D.F. Brazil, CEP 70.910-900. 2Institute of Tropical Medicine at Sao Paulo University Av. Enéas de Carvalho Aguiar, 500/prédio IMT II/3º andar. São Paulo, SP. Brazil, CEP 05403-000.

Abstract:The primate T cell lymphotropic virus group comprises pathogenic and apathogenic agents found in human and simian hosts. Up to date, three types of the simian T cell lymphotropic virus/STLV and four types of the human T cell lymphotropic virus/HTLV have been isolated and characterized from non human primates and from human hosts respectively.

We have not found evidences of STLV-1 infection among new world monkeys and besides findings of HTLV-1 and HTLV-2 infection among brazilian mixed ethnic populations and Amerindians respectively, some unresolved HTLV indeterminate-Western blot results prevailed among human groups of different ethnic background. Based on recent serologic detection, isolation and characterization of HTLV-3 and HTLV-4 among African populations in central Africa and additional unrefutable evidences of early human migration from Africa and Australia to the American continent previously of Asiatic population migration lead us to hypothesize that human descendents of mixed Amerinds and Africans or remaining Africans explain the very frequent presence of Western blot-indeterminate results for HTLV-1/2 that we and other groups have been detecting and also the unusual absence of HTLV-2 infection among some relatively homogeneous ethnic native human populations in the American continent.

Keywords: deltaretrovirus, human T cell lymphotropic virus, simian T cell lymprotropic virus, amerindians, human

migration

Introduction

Recently Kanzaki and Casseb [1] described the unusual finding of HTLV-1 infection among Waiãpi

Amazonian Amerindians. Also, among certain ethnic ancient groups, in the American Continent, it is

very low the prevalence of both, HTLV-1 and HTLV-2 infection [2–5]. Colin et al. [6] found a very low

prevalence to HTLV-1/2 infection in a human population in the Occidental Amazon (Acre/Brazil) despite

other works showing high prevalence to HTLV-2 among Amerindian groups mainly in South America [1].

Besides these findings, not so common among Amerindians, we and others have also found frequently

HTLV-1/2 seroreactors by the Enzyme-linked immunosorbent assay /Immunofl uorescence (ELISA/IF)

unconfirmed by the Western blot analysis, but exhibiting isolated bands to one peptide or glycopeptide

apparently related to deltaretroviruses [1,7,8]. In the beginning of the pioneering HTLV epidemiological

studies in Brazil, we suspected that the high incidence of HTLV-2 among some Amerindian ethnicities

were related to a deltaretrovirus circulating among new world monkeys; therefore in order to

corroborate this hypothesis we screened amazonian monkeys (58 Cebus paella, 5 Cebus albifrons,

5 Cebus nigrivitatus, 6 Callicebus moloch, 13 Callithrix jaccus jacchus, 1 Callithrix argentata argentata,

34 Aotus agarae infulatus, 2 Alouata belzebu belzebu and 10 Chiropotes satanas utahicki) for

HTLV-1/2/STLV-1 antibodies by the ELISA test and found none reactive but we had 6 out of 24 african

old world monkeys, Cercopithecus aethiops, highly reactive by the ELISA assay [7]. Other authors also

could not find HTLV-1/STLV-1 antibodies among new world monkeys [9,10] and confirming that new

world monkeys are not susceptible to HTLV-1 infection, new world squirrel monkeys (Saimiri sciureus)

were experimentally infected by HTLV-1 infected cells as apparently these animals did not share cell

receptors for the virus [11]. Despite Chen et al. [12] claims of STLV-2 isolation from Ateles fusciceps,

a new world monkey in Panama, nobody else could demonstrate antibodies among new world monkeys

neither isolate the virus again. Most of these HTLV-1 strains are serologically indistinguishable from

Correspondence: Luis Isamu Barros Kanzaki, SQN 206. BLOCO B. Apartment 403. ASA Norte. Brasilia,

D.F. Brazil, CEP 70844-020. Tel: 55 61 38790007/Mobile: 55 61 81387917; Email: kanzaki@unb.br

Retrovirology: Research and Treatment 2008:1 15–20

STLV-1 strains, as their viral genomes exhibit about 96% nucleotide homology which allow us to easily detect STLV-1 antibodies utilizing serologic assays sensitized with HTLV-1 peptides [13]. Presently, it is assumed that the deltaretroviruses evolution occurred in Africa and very probably after the branching of new and old world monkeys' ancestors [13,14].

According to different authors, during the Pleistocene/Holocene transition period, at least two different human populations migrated to the American Continent. Cranial anatomic analysis recognized two peculiar human morphologic patterns related to Asiatics and Africans, so contrary to the common sense, one of these groups, the Asiatics were not the first human groups to migrate to the America continent, but the African group, probably coming from Oceania and/or Africa. Confi rming these findings, Neves et al. [15] emphasizes that the colonization of the New World occurred by two distinct, succeeding biological populations: an early one with a cranial morphology similar to that found today in the African and Australian continents, and a later one with a morphology similar to that found today among northeastern Asians.

Neves et al. [16] also have been finding

increasing skeletal evidences from U.S.A., Mexico, Colombia, and Brazil strongly suggesting that the first settlers in the Americas had a cranial morphology distinct from that displayed by most late and modern native Americans.

Based on these research results and our unusual findings of HTLV-1 infection among Amazonian amerinds, and indeterminate-Western blot profiles, we hypothesized that early human populations, the Australo-Melanesians and Africans that colonized the American continent 12.000–35.000 years in the past, previously to the migration of asian populations, by some way were not susceptible to HTLV-1 and 2 infection, and probably were mainly infected by other human deltaretroviruses.

The Primate T cell Lymphotropic Viruses

The Human T cell Lymphotropic Viruses are exogenous deltaretroviruses comprising four types, HTLV-1 to HTLV-4 [17–20]. The HTLVs and the Simian T Lymphotropic Viruses (STLVs) altogether are commonly denominated the Primate T Lymphotropic Viruses (PTLVs) due to their high

nucleotide homology besides their common general genomic organization [21–23]. They were numbered according to their discoveries, not denotating the hierarchic fi logenetic positioning.

Epidemiological and molecular studies point out to Africa as the motherland of these biological entities, which spread out to Asia, Europe and Oceania accompanying their hosts in their migrations [22,23].

Human Deltaretroviruses Evolution and Human Disease

As the deltaretroviruses are closely associated to the cell, their transmission mode are generally enclosed in familiar clusters, being transmitted by sexual intercourse, usually from man to woman and during breast-feeding, from mother to lactating children [24,25]. Their low mutation rate also confer them the maintenance of low pathogenicity behavior or depending on the type, their apathogenic role, therefore they are very successfully horizontally transmitted throughout generations [26,27]. Nevertheless, the human cultural development accompanied by population growth which consequently moved huge mass of people to more developed towns adding high levels of demographic density imposing exaggerated levels of stress and besides these factors, the advances in preventive and curative medicine have selected all kind of microorganisms by the survival of their human hosts. Also, climatic changes with elevated exposition to different wave length radiations, mainly ionizing radiation, have played an important role in the mutation rate of all kind

of genetic elements in acellular and cellular organisms [28]. Henceforth, taking in account all the facts mentioned, evolution has been in fast course and ultimately it seems to be in a rush at least in our knowledge of the modern civilization, in a way that apathogenic deltaretroviruses have been claimed to be involved in a large spectrum of diseases [29]. Comparing the human and deltaretrovirus genome from different time points, we can assume that the virus in a general way did not change at all, but human populations became much more vulnerable now than in the past to different microorganisms. Different vaccines, a lot of new chemical drugs and modern curative measures have been selecting less adapted human beings, so in these subjects the immune system does not respond appropriately, and an example of it are the

autoimmune diseases associated to HTLV-1 infection among human beings [29–32].

Primate Deltaretroviruses

Geographical Segregation

The emergence of STLVs after the evolutionary splitting of non human primates into new world and old world species avoided the spreading of STLVs to the American continent [22,23]. Several seroepidemiological studies in primate centres in the American continent could not fi nd STLV-1 infection among new world monkeys.

It is interesting to note the distribution and segregation of HTLV-1 and HTLV-2 in cosmopolitan megalopolis and small towns in rural areas respectively, around the world [1,2,8,33]. Among Amerindian communities, HTLV-2 infection is widely spread out while HTLV-1 infection is mainly found among communities of African and Japanese origin, eventhough the intense human miscegenation in countries like Brazil, contributes to equal distribution of both HTLV types in human population as also, in the U.S. the epidemic HTLV-2 transmission among intravenous drug users changed the usual distribution pattern of human deltaretroviruses among different human ethnicities [8,33,34]. Examining HTLV-1 distribution

in the world, historical facts try to explain the virus dissemination carried by their African hosts, in Portuguese commercial ships navigating to India and Japan, and lately in the slave trade period to the American continent and Caribbean basin. High levels of HTLV-1 prevalence is found in the Caribbean basin and Brazil among afrodescendents [35].
In Japan, the high HTLV-1 prevalence is not well understood as initially proposed by Africans transportation in Portuguese trade ships in Japan [36].
Noteworthy to mention that STLV-1 is endemic among protected simians, Macaca fuscata, in japanese sanctuary mountains. Also, HTLV-1 is more related to the African strain of STLV-1 than to the Japanese strain. Would be the origin of HTLV-1 high incidence in Japanese human populations explained by STLV-1 natural human infection transmitted from Macaca fuscata? [37] Or by very ancient invasion of Japan archipellagus by paleo-Mongoloids human lineages more than

10.000 years ago? [38]. By analogy to what is believed about SIV transmission from chipanzees to man and SIV mutation/adaptation to human target cells, generating HIV-1/2, which demanded a large step, while in the case of a possible transmission of STLV-1 from simians to man, would be a short step as both viruses, STLV-1 and HTLV-1 share about 96% nucleotide homology.

Particularly in Brazil, HTLV-1 prevalence is

widespread, but mainly concentrates among black communities that arrived in Brazil during the slave trade period, contrasting to HTLV-2 prevalence which is high among Amerindian communities and intravenous drug users [39]. Despite this common sense, some exceptions occur, as the fi nding of HTLV-1 low prevalence among some Amerindian communities and any known reactivity to HTLV-2 peptides [1]. Reviewing the literature, it seems that not only Amerindians colonized the American continent, but other ethnic groups have arrived earlier in the new world. The most antique of these human groups were Australo-Melanesians African descendents. Despite remnants findings of these human groups spread out all over the continent, mainly abundant in Brazil, there seems actually to be vanished, nevertheless it is believed that few of them mixed to some other populations. Apparently the arrival of Asians to the continent through the Behring strait and the total occupation from north to south, must have anhilated the first human settlers in the American continent and as a common practice, very probably women and children became prisoners and mixed to the conquerors [15,16].

HTLV-1 and HTLV-2 Differences

When we look at the distribution of deltaretroviruses among human populations, it apparently means that ethnic pattern would determine which HTLV type

would be housed by the host [35,36]. As previously mentioned, HTLV-2 is mainly disseminated among native Americans of asian origin, from North to South America [33,34,36,37,38] but curiously, some of these Amerindians groups exhibit low levels of HTLV-2 infection or do not express the virus at all in their cells [1,6]. How close are different human ethnic groups? Are genetic or cultural factors or both involved in more or less susceptibility to HTLVs infection? [34–36] Are these differences related to the levels of HTLV-1 or 2 infection susceptibility? [37,38]. Are so polymorphic the cell receptors for these viruses? [39] Anyway, why HTLV-1 is not reported to be well disseminated among intravenous drug users as it happens with HTLV-2? Would be their different biological behavior? It is very rare to

observe clinical diseases related to HTLV-2 infection, but the frequency of HTLV-1 related disease occurrence is higher compared to HTLV-2. Genomic organization of both viruses are similar, but their cell targets are different [40,41]. While HTLV-1 preferentially infects CD4+ cells, HTLV-2 exhibits CD8+ tropism. As it is well known, CD4+ cells are functionally more important than CD8+ cells, which mainly exerts a fi nal effector function as a cytotoxic cell. [42,43].

Hypotheses

In all seroepidemiological surveys we have conducted among Amerindian communities and mixed ethnic populations, there is a high frequency of indeterminate Western blot results [1,7]. Reviewing the literature, recently, two new HTLV types were identified in Africa, HTLV-3 and HTLV-4, and curiously, in serological assays screening for HTLV-1 and 2 antibodies, people infected by HTLV-3 or 4, displayed Western blot isolated bands similarly to indeterminate results as we have found among our samples [17–19]. Future studies would corroborate these assumptions and would reinforce our hypothesis of vestiges of Australo-Melanesians and africans among our isolated native communities, explaining therefore the unusual absence of HTLV-2 infection among

some Amerindian communities, interfered by HTLV-3/4 infection.

Conclusion

Unusual finding of HTLV-1 infection among some Amerindian communities and in some cases, the absence of HTLV-2 infection among some other Amerindian communities besides the frequency of indeterminate-Western blot bands to HTLV-1 and 2 antibodies, strongly suggest the circulation of other deltaretroviruses among Amerindians and mixed ethnic populations in the American continent. Also, we have associated this hypothesis to the recent theory of earlier Australo-Melanesians and African descendents migrations to the American continent, carrying with them HTLV-3 and 4. Very probably remnants of these populations or the dominance of their HLA alleles in the mixed descendents could be responsible for immune response to HTLV-3/4 yielding interference to HTLV-1/2 infection (44–48). As previously discussed, HTLV-1/2 transmission in nuclear families would determine viral antigens immune

tolerance as earlier proposed by Medawar (1983), mainly among newborn [49], but later, 40 or 50 years, a small percentage of these infected subjects would develop an HTLV-1 related disease, as tolerance would break up, favored by the immune system aging associated to a number of

environmental factors exposure.

Our preliminary studies corroborated by others could not support the initial hypothesis in the early epidemiological studies in Brazil of a possible transmission of a deltaretrovirus from new world monkeys to native Amazonians. Until now, any known deltaretrovirus has not yet been isolated from new world monkeys.

Acknowledments

This work is specially dedicated to Dr. Koshi Maruyama, Dr. Laura Trejo-Avila and Dr. Reyes Tamez-Guerra.

Disclosure

The authors report no conflicts of interest.

References

[1]
Kanzaki, LIB. and Casseb, J. 2007. Unusual Finding of HTLV-I Infection Among Amazonian Amerindians. Arch. Med. Res., 38:897–900.

[2]
Gongora-Biachi, R.A., Lal, R.B., Rudolph, D.L., Castro-Sansores, C., Gonzalez-Martinez, P. and Pavia-Ruz, N. 1997. Low prevalence of HTLV-II in Mayan Indians in the Yucatan Peninsula, Mexico. Arch. Med. Res., 28(4):555–8.

[3]

Trejo-Avila, L.M., Fuentes-Pensamiento, R., Socorro Flores-Castañeda, M., Diaz-Mendoza, M.L., Zapata-Benavides, P. and Tamez-Guerra, R.S. 1996. Seroprevalence of HTLV-I/II in blood donors in Monterrey, Mexico. Arch. Med. Res., 27(1):97–9.

[4]

Gongora-Biachi, R.A., Gonzalez-Martinez, P., Puerto, F.I., Sosa-Muñoz, J., Duarte-Zapata, L., Bastarrachea-Ortiz, J., Yamaguchi, K., Nishimura, Y. and Takatsuki, K. 1992. A low prevalence of HTLV-I/-II infection among eight population groups from Merida Yucatan, Mexico. J. Acquir. Immune. Defi c. Syndr., 5(1):104–6.

[5]

Flores-Castañeda, M.S., Salinas-Carmona, M.C., Leal-González, C., Y.áñez-Rodríguez, A. and Trejo-Avila, L.M. 1992. Antibodies against human T-cell lymphotropic viruses in subjects at high risk for HIV in Monterrey. Rev. Invest. Clin., 44(1):37–41.

[6]

Colin, D.D., Alcântara J.únior, L.C., Santos, F.L., Uchôa, R. and Tavares-Neto, J. 2003. Seroprevalence of human T cell lymphotropic virus infection and associated factors of risk in blood donors of Rio Branco city, AC, Brazil (1998-2001). Rev. Soc. Bras. Med. Trop., 36(6):677–83.

[7]

Kanzaki, LIB. 1995. Epidemiologia del HTLV en la Amazonia brasileña: Seroprevalencia e identificacion del vírus circulante. Doctoral thesis. Monterrey, Nuevo Leon, Mexico.

[8]

Shindo, N., Alcantara, L.C., Van Dooren, S., Salemi, M., Costa, M.C., Kashima, S. et al. 2002. Human retroviruses (HIV and HTLV) in Brazilian Indians: seroepidemiological study and molecular

epidemiology of HTLV type 2 isolates. AIDS Res. Hum. Retroviruses,

18:71–7.

Retrovirology: Research and Treatment 2008:1

HTLV distribution among native americans and early African migration

[9] Kaplan, J.E., Holland, M.U., Green, D.B., Gracia, F. and Reeves, W.C. [26] Azran, I., Schavinsky-Khrapunsky, Y., Priel, E., Huleihel, M. and

1993. Failure to detect human T-lymphotropic virus antibody in Aboud, M. 2004. Implications of the evolution pattern of human

wild-caught New World primates. Am. J. Trop. Med. Hyg., T-cell leukemia retroviruses on their pathogenic virulence (Review).

49(2):236–8. Int. J. Mol. Med., 14(5):909–15.

[10] Andrada-Serpa, M.J., Tosswill, J., Schor, D., Linhares, D., Dobbin, J. [27] Van Dooren, S., Pybus, O.G., Salemi, M., Liu, H.F., Goubau, P.,

and Pereira, M.S. 1989. Seroepidemiologic survey for antibodies to Remondegui, C. et al. 2004. The low evolutionary rate of human

human retroviruses in human and non-human primates in Brazil. Int. T-cell lymphotropic virus type-1 confirmed by analysis of vertical

J. Cancer, 44(3):389–93. transmission chains. Mol. Biol. Evol., 21(3):603–11.

[11] Kazanji, M. 2000. HTLV type 1 infection in squirrel monkeys (Saimiri [28] Barros Kanzaki, L.I. 2006. Hypothetical HTLV-I induction by ionizing

sciureus): a promising animal model for HTLV type 1 human radiation. Med. Hypotheses, 67(1):177–82.

infection. AIDS Res. Hum. Retroviruses, 16(16):1741–6. [29] Ohshima, K. 2007. Pathological features of diseases associated with

[12] Chen, Y.M., Jang, Y.J., Kanki, P.J., Yu, Q.C., Wang, J.J., Montali, R.J., human T-cell leukemia virus type I. Cancer Sci., 98(6):772–8.

Samuel, K.P. and Papas, T.S. 1994. Isolation and characterization of [30] Akimoto, M., Matsushita, K., Suruga, Y., Aoki, N., Ozaki, A.,

simian T-cell leukemia virus type II from New World monkeys. Uozumi, K. et al. 2007. Clinical manifestations of human

J. Virol., 68(2):1149–57. T lymphotropic virus type I-infected patients with systemic lupus

[13] Van Dooren, S., Salemi, M. and Vandamme, A.M. 2001. Dating the erythematosus. J. Rheumatol., 34(9):1841–8.

origin of the African human T-cell lymphotropic virus type-i (HTLV-I) [31] Lalive, P.H., Allali, G. and Truffert, A. 2007. Myasthenia gravis

subtypes. Mol. Biol. Evol., 18(4):661–71. associated with HTLV-I infection and atypical brain lesions. Muscle

[14] Vandamme, A.M., Liu, H.F., Van Brussel, M., De Meurichy, W., Nerve, 35(4):525–8.

Desmyter, J. and Goubau, P. 1996. The presence of a diver[

32] Matsuda, T., Tomita, M., Uchihara, J.N., Okudaira, T., Ohshiro, K.,

gent T-lymphotropic virus in a wild-caught pygmy chimpan-Tomoyose, T. et al. 2005. Human T cell leukemia virus type I-infected

zee (Pan paniscus) supports an African origin for the human patients with Hashimoto's thyroiditis and Graves' disease. J. Clin.

T-lymphotropic/simian T-lymphotropic group of viruses. J. Gen. Endocrinol. Metab., 90(10):5704–10.

Virol., 77(Pt 5):1089–99. [33] Vrielink, H. and Reesink, H.W. 2004. HTLV-I/II prevalence in different

[15] Neves, W.A., Hubbe, M. and Piló, L.B. 2007. Early Holocene human geographic locations. Transfus. Med. Rev., 18(1):46–57.

skeletal remains from Sumidouro Cave, Lagoa Santa, Brazil: history [34] Barquera, R., Zúñiga, J., Hernández-Díaz, R., Acuña-Alonzo, V.,

of discoveries, geological and chronological context, and comparative Montoya-Gama, K., Moscoso, J. et al. 2008. HLA class I and class II

cranial morphology. J. Hum. Evol., 52(1):16–30. haplotypes in admixed families from several regions of Mexico. Mol.

[16] Neves, W.A., Hubbe, M., Okumura, M.M., González-José, R., Immunol., 45(4):1171–8.

Figuti, L., Eggers, S. and De Blasis, P.A. 2005. A new early Holocene [35] Alcantara, Jr L.C., Van Dooren, S., Gonçalves, M.S., Kashima, S.,

human skeleton from Brazil: implications for the settlement of the Costa, M.C., Santos, F.L. et al. 2003. Globin haplotypes of human

New World. J. Hum. Evol., 48(4):403–14. T-cell lymphotropic virus type I-infected individuals in Salvador,

[17] Callatini, S., Chevalier, S.A., Duprez, R., Bassot, S., Froment, A., Bahia, Brazil, suggest a post-Columbian African origin of this virus.

Mahieux, R. and Gessain, A. 2005. Discovery of a new human T-cell J. Acquir. Immune. Defi c. Syndr., 33(4):536–42.

lymphotropic virus (HTLV-3) in Central Africa. Retrovirology, 2:30. [36] Fleming, A.F. 1984. HTLV from Africa to Japan. Lancet,

[18] Mahieux, R. and Gessain, A. 2005. New human retroviruses: 1(8371):279.

HTLV-3 and HTLV-4. Med. Trop (Mars), 65(6):525–8. [37] Melbye, M., Poulsen, A.G., Gallo, D., Pedersen, J.B., Biggar, R.J.,

[19] Switzer, W.M., Qari, S.H., Wolfe, N.D., Burke, D.S., Folks, T.M. and Larsen, O. et al. 1998. HTLV-1 infection in a population-based cohort

Heneine, W. 2006. Ancient origin and molecular features of the novel of older persons in Guinea-Bissau, West Africa: risk factors and

human T-lymphotropic virus type 3 revealed by complete genome impact on survival. Int. J. Cancer, 76(3):293–8.

analysis. J. Virol., 80(15):7427–38. [38] Miura, T., Fukunaga, T., Igarashi, T., Yamashita, M., Ido, E., Funa[

20] Van Dooren, S., Salemi, M. and Vandamme, A.M. 2001. Dating the hashi, S. et al. 1994. Phylogenetic subtypes of human T-lymphotropic

origin of the African human T-cell lymphotropic virus type-i (HTLV-I) virus type I and their relations to the anthropological background.

subtypes. Mol. Biol. Evol., 18(4):661–71. Proc. Natl. Acad. Sci. U.S.A., 91(3):1124–7.

[21] Wolfe, N.D., Heneine, W., Carr, J.K., Garcia, A.D., Shanmugam, V., [39] Alcantara, L.C., Shindo, N., Van Dooren, S., Salemi, M., Costa, M.C.,

Tamoufe, U., Torimiro, J.N., Prosser, A.T., Lebreton, M., Kashima, S. et al. 2003. Brazilian HTLV type 2a strains from

Mpoudi-Ngole, E., McCutchan, F.E., Birx, D.L., Folks, T.M., intravenous drug users (IDUs) appear to have originated from two

Burke, D.S. and Switzer, W.M. 2005. Emergence of unique primate sources: Brazilian Amerindians and European/North American IDUs.

T-lymphotropic viruses among central African bushmeat hunters. AIDS Res. Hum. Retroviruses, 19(6):519–23.

Proc. Natl. Acad. Sci. U.S.A., 102(22):7994–9. [40] Stilianakis, N.I. and Seydel, J. 1999. Modeling the T-cell

[22] Van Dooren, S., Verschoor, E.J., Fagrouch, Z. and Vandamme, A.M. dynamics and pathogenesis of HTLV-I infection. Bull. Math. Biol.,

2007. Phylogeny of primate T lymphotropic virus type 1 (PTLV-1) 61(5):935–47.

including various new Asian and African non-human primate strains. [41] Kinet, S., Swainson, L., Lavanya, M., Mongellaz, C., Montel-Hagen,

Infect. Genet. Evol., 7(3):374–81. A., Craveiro, M. et al. 2007. Isolated receptor binding domains of

[23] Slattery, J.P., Franchini, G. and Gessain, A. 1999. Genomic evolution, HTLV-1 and HTLV-2 envelopes bind Glut-1 on activated CD4+ and

patterns of global dissemination, and interspecies transmission of CD8+ T cells. Retrovirology, 4:31.

human and simian T-cell leukemia/lymphotropic viruses. Genome. [42] Manel, N., Taylor, N., Kinet, S., Kim, F.J., Swainson, L., Lavanya, M.

Res., 9(6):525–40. et al. 2004. HTLV envelopes and their receptor GLUT1, the

[24] Roucoux, D.F., Wang, B., Smith, D., Nass, C.C., Smith, J., ubiquitous glucose transporter: a new vision on HTLV infection?

Hutching, S.T., Newman, B., Lee, T.H., Chafets, D.M. and Murphy, E.L. Front Biosci., 9:3218–41.

2005. HTLV Outcomes Study Investigators. A prospective study of [43] Takenouchi, N., Jones, K.S., Lisinski, I., Fugo, K., Yao, K.,

sexual transmission of human T lymphotropic virus (HTLV)-I and Cushman, S.W. et al. 2007. GLUT1 is not the primary binding receptor

HTLV-II. J. Infect. Dis., 191(9):1490–7. but is associated with cell-to-cell transmission of human T-cell

[25] Moriuchi, M. and Moriuchi, H. 2006. Induction of lactoferrin gene leukemia virus type 1. J. Virol., 81(3):1506–10.

expression in myeloid or mammary gland cells by human T-cell [44] Maiers, M., Gragert, L. and Klitz, W. 2007. High-resolution HLA

leukemia virus type 1 (HTLV-1) tax: implications for milk-borne alleles and haplotypes in the United States population. Hum.

transmission of HTLV-1. J. Virol., 80(14):7118–26. Immunol., 68(9):779–88.

[45]

Tibayrenc, M. 2007. Human genetic diversity and the epidemiology of parasitic and other transmissible diseases. Adv. Parasitol., 64:377–422.

[46]

Derse, D., Hill, S.A., Princler, G., Lloyd, P. and Heidecker, G. 2007. Resistance of human T cell leukemia virus type 1 to APOBEC3G restriction is mediated by elements in nucleocapsid. Proc. Natl. Acad. Sci. U.S.A., 104(8):2915–20.

[47]

Pontes, G.S., Tamegão-Lopes, B., Machado, L.F., Azevedo, V.N., Ishak, M.O., Ishak, R. et al. 2005. Characterization of mannose-binding lectin gene polymorphism among human T-cell lymphotropic virus 1 and 2-infected asymptomatic subjects. Hum. Immunol., 66(8):892–6.

[48]

Kinet, S., Swainson, L., Lavanya, M., Mongellaz, C., Montel-Hagen, A., Craveiro, M. et al. 2007. Isolated receptor binding domains of HTLV-1 and HTLV-2 envelopes bind Glut-1 on activated CD4+ and CD8+ T cells. Retrovirology, 4:31.

[49]

Medawar, P.B. and Hunt, R. 1983. Can. fetal antigens be used for prophylactic immunization?. Ciba. Found Symp., 96:160–81.