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Review Article

HTLV-1 and the Host Immune System : How the Virus Disrupts Immune Regulation, Leading to HTLV-1 Associated Diseases

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Human T-cell leukemia virus type 1 (HTLV-1) was the first retrovirus shown to cause human diseases, such as adult T-cell leukemia (ATL) and HTLV-1 associated myelopathy/tropic spastic paraparesis (HAM/TSP). Despite extensive study for three decades, it remains elusive how HTLV-1 induces these diseases. HTLV-1 mainly infects CD4 T cells, inducing dysregulation of the host immune system. Recent studies have uncovered the mechanisms of differentiation and function of CD4 T cells at the cellular and molecular levels, extending our understanding of the pathological conditions associated with HTLV-1 infection. This review focuses on recent advances in our understanding of the interaction between HTLV-1 and the host immune system, which should provide us a clue to the mechanisms of HTLV-1 mediated pathogenesis. 〔*J Clin Exp Hematopathol 50(1) : 1-8, 2010*〕

Keywords: human T-cell leukemia virus type 1, adult T-cell leukemia, human T-cell leukemia virus type 1 bZIP factor, chronic viral infection, regulatory T cells

INTRODUCTION

Human T-cell leukemia virus type 1 (HTLV-1) is a complex retrovirus that may have been transmitted to humans from monkeys more than ten thousands years ago.[1] The human host has several immune mechanisms that eliminate foreign pathogens, and like other successful pathogens, HTLV-1 must have strategies for evading the host immune response. Like human immunodeficiency virus (HIV), HTLV-1 mainly infects CD4 T cells, which are the central regulators of the acquired immune response. To establish persistent infection, HTLV-1 perturbs the regulation of CD4 T cells, sometimes leading to adult T-cell leukemia (ATL)[2,3] (Fig. 1) or sometimes leading to chronic inflammatory diseases such as HTLV-1 associated myelopathy/tropic spastic paraparesis (HAM/TSP),[4] uveitis,[5] arthritis,[6] and alveolitis.[7]

Since the discovery of HTLV-1, extensive studies have been performed using various experimental approaches. However, the nature of HTLV-1 pathogenesis still remains elusive. This problem is a serious obstacle to establishing effective therapies for HTLV-1 associated diseases.

Precise insight into HTLV-1 mediated pathogenesis requires careful consideration of the host cells and the effect HTLV-1 has on them. Thus in this review, we focus on the interaction between HTLV-1 and the host immune system. We believe that understanding this interaction will be helpful for understanding the pathogenesis of HTLV-1 associated diseases.

Preferential expansion of HTLV-1-infected CD 4 T cells

After the entry of a retrovirus into a host cell, the viral genomic RNA is reverse transcribed into a double strand DNA form and integrated into the host chromosomal DNA. The integrated virus, known as a provirus, expresses viral genes to achieve further transmission. HTLV-1 is widely believed to replicate primarily not as free viral particles, but as provirus, by inducing the proliferation of infected host cells.[3,8] Although HTLV-1 can infect various kinds of cells, such as dendritic cells, B cells, macrophages, and T cells,[9] the virus preferentially induces the clonal expansion of CD4 T cells.[10,11] This clonal expansion is presumed to be related to the transformation of infected CD4 T cells in some carriers.

The proliferation of infected host CD4 T cells is thought to be induced by viral accessory or regulatory proteins (Fig. 2). Many studies have focused on a viral protein, Tax, and much has been learned about its functions.[12,13] Tax is a transcriptional co-factor, and hijacks many signaling pathways

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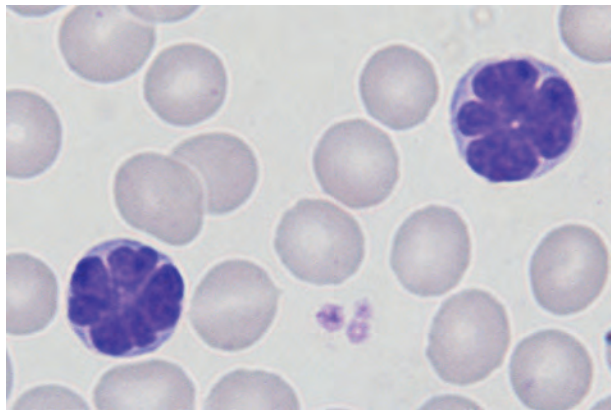

Fig. 1. Morphological findings of typical ATL cells. ATL cells with lobulated nuclei are called as "flower cells".

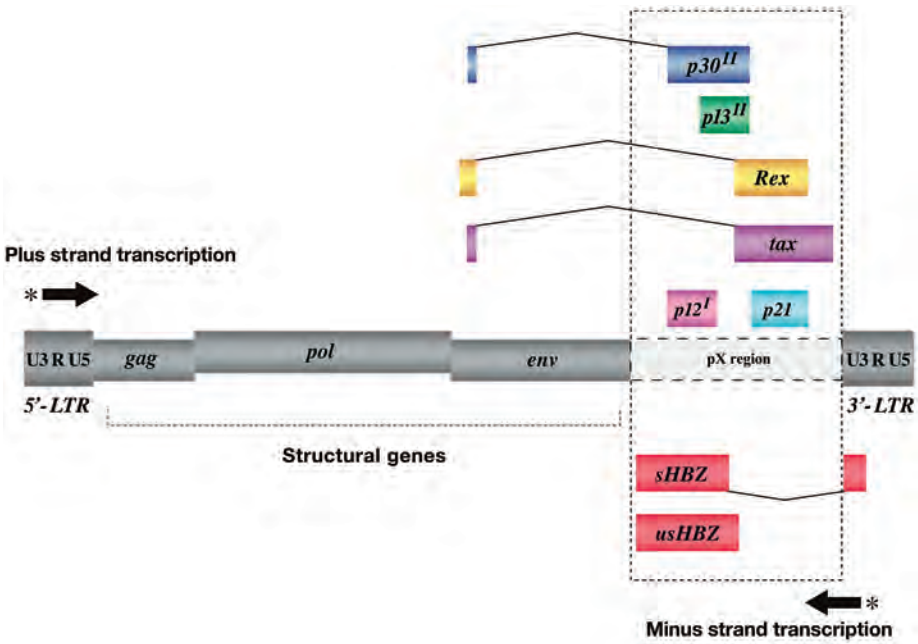

Fig. 2. The structure of HTLV-1. HTLV-1 encodes accessory and regulatory genes in the pX region as well as viral structural genes.

related to anti-apoptosis or cell proliferation (Fig. 3). Therefore Tax is widely considered a major player in inducing the proliferation of infected cells as well as in the transforming activity of HTLV-1. But at the same time, Tax is known as a major target of the host immune system.[14,15] The expression of Tax in the host cell induces attack by cytotoxic T lymphocyte (CTLs), resulting in the elimination of the infected cell. In line with this notion, the expression of Tax seems to be reduced during the process of the leukemogenesis,[16] suggesting that Tax expression is disadvantage for the survival of infected cells, at least in immune competent individuals.

Another viral gene encoding the HTLV-1 bZIP factor (HBZ) was recently identified,[17] and subsequently a novel splice isoform was identified by three different groups independently.[18-20] More recent reports showed that the new splice isoform of the transcript is not only more abundant but also functionally more important than the other type of transcript.[21,22] HBZ is reported to have an effect on the increased proliferation of infected cells.[20,23] However, HBZ has been shown to suppress the transcriptional activity of c-Jun[24,25] and the classical pathway of NF-κB[26] *in vitro*, indicat-

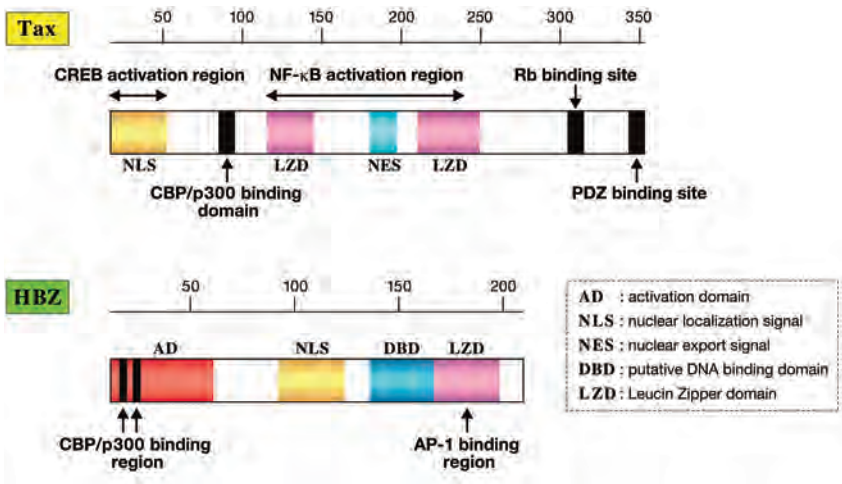

Fig. 3. The schematic structure of viral proteins, Tax and HBZ. Both Tax and HBZ play crucial roles in the HTLV-1 pathogenesis by interacting cellular factor as shown in this figure.

ing that HBZ protein is unlikely to stimulate cell proliferation *in vitro* (Fig. 3). Consistent with this notion, the deletion of the HBZ gene in a molecular clone of HTLV-1 had no influence on its *in vitro* transforming activity.[27] On the other hand, HBZ RNA stimulates cell proliferation when over-expressed *in vitro*.[20] The fact that HBZ is a constitutively expressed viral gene suggests that it has a role indispensable to the survival of HTLV-1 *in vivo*,[20,21] yet further experiments are required to elucidate the molecular function of HBZ or its role in HTLV-1 related pathogenesis. At the present time, it is controversial how HTLV-1 specifically induces the clonal expansion of CD4 T cells, but this CD4 specific function of HTLV-1 must be an important clue to the pathogenesis of ATL and HTLV-1 related chronic inflammatory diseases.

HTLV-1 and CD 4 T cell subsets including Foxp3$^+$regulatory T (Treg) cells

When ATL was established as a distinct clinical entity, there was little information available about the host cells beyond the fact that they were T cells.[28] Progress in immunology has now led to a more detailed understanding of T-cell subsets. Furthermore, the mechanisms regulating T-cell differentiation, activation, and function have now been better elucidated. Thus it is time for us to re-evaluate the influence of HTLV-1 infection on CD4 T cells.

ATL cells are typically CD4$^+$CD25$^+$ T cells, a fact which initially suggested that ATL cells was derived from activated T cells.[29] Therefore, in addition to resting peripheral blood mononuclear cells (PBMCs), phytohemagglutinin (PHA) stimulated cells have been used as normal counterparts of ATL cells for various experiments. Later, CD4$^+$CD25$^+$ T cells were also considered to act as regulatory T cells (T_{reg} cells) that function to suppress excessive immune responses.[30] Within the CD4$^+$CD25$^+$ T cell subset, it was impossible to distinguish T_{reg} cells from activated T cells until the identification of Foxp3 as a T_{reg} "master switch." Several groups independently reported that Foxp3 plays crucial roles in the differentiation, function, and homeostasis of T_{reg} cells.[31-33] Most ATL cells are CD4$^+$CD25$^+$Foxp3$^+$, indicating that they may be derived from T_{reg} cells.[34,35] The accumulation of Foxp3$^+$ATL cells could be a possible reason for the immune compromised status frequently observed in ATL cases,[36] yet some ATL cells lost regulatory functions.[37-39] As Foxp3 has important roles for T_{reg} cell function, a report that Foxp3$^+$ ATL cells had lower Foxp3 expression levels when compared with normal Foxp3$^+$ T_{reg} cells indicates that the suppressive function is impaired in such ATL cells.[35] To further complicate the picture, the stimulation of naïve human CD4 T cells transiently induces the expression of Foxp3,[40] indicating that the Foxp3$^+$ ATL cells could possibly be derived from such an activated cell population. Conversely, a recent study indicated that Foxp3$^+$ T_{reg} cells have plasticity : thus Foxp3$^+$ T_{reg} cells can convert to Foxp3 negative cells.[41] This report indicates the possibility that Foxp3 negative ATL cells might come from T_{reg} cells that formerly expressed Foxp3. The immunohistochemical finding that Foxp3 expression is heterogeneous in some ATL lymph nodes may reflect this plasticity of Foxp3 expression in T_{reg} cells.[36]

The HTLV-1 viral protein Tax is reported to suppress Foxp3 expression at the transcriptional level when over-expressed in primary human CD4 T cells.[42] This indicates that Tax can influence the expression of Foxp3 in HTLV-1 infected T_{reg} cells. These data collectively suggest that under-

standing Foxp3$^+$ T_{reg} cells as an important subpopulation of CD4 T cells is important for elucidating the leukemogenesis of ATL by HTLV-1, yet further experiments are required to address precisely how HTLV-1 disturbs the homeostasis of T_{reg} cells.

To understand the pro-inflammatory properties of HTLV-1, it is important to consider another subset of the T cell population : inflammatory effector T cells. Previous reports suggest that HTLV-1 infection reduces the fraction of naïve T cells,[43] whereas HTLV-1 is enriched in CD4$^+$CD45RO$^+$ effector/memory CD4 T cells.[11] It remains unknown whether the shift from naïve to effector/memory T cells results from systemic pro-inflammatory circumstances or a CD4 T-cell intrinsic effect of HTLV-1 infection. HTLV-1 infection enhances not only the generation of effector/memory CD4 T cells but also increase the proliferation of the CD4 T cell subset,[44] indicating that CD4 T cells are continuously activated *in vivo*. Such activated CD4 effector T cells may migrate into the tissues, i.e., central nervous system, joints, lung, or uvea, in genetically susceptible individuals, leading to inflammation like that seen with certain autoimmune diseases.[45] Since CD4 T cells are the predominant cells detected in early inflammatory lesions,[46] activation of CD4 T cells is likely one of major contributors to HTLV-1-induced inflammation. Among the various effector functions of CD4 T cells, hyper-production of IFN-γ is widely believed to contribute to the onset of HTLV-1 mediated chronic inflammation.[47,48] Th_1 cells, a major subset of CD4 T cells, are characterized by their ability to produce IFN-γ. In addition to Th_1 cells, a recently identified Foxp3$^+$ subset, CD4$^+$CD45RA$^-$Foxp3^{low} non-T_{reg} cells, also have the potential to produce various inflammatory cytokines, such as IFN-γ, IL-4, and IL-17.[49,50] HTLV-1 may disturb the infected CD4 T-cell differentiation and function in cell-intrinsic manner (Fig. 4). Unraveling the picture require a two-pronged approach : learning more *in vivo* about the status and functioning of CD4 T cells during HTLV-1 infection, and ascertaining *in vitro* the molecular mechanisms by which HTLV-1 disturbs their differentiation, function, and homeostasis. A better understanding of how HTLV-1 causes inflammation should help us to establish therapeutic or preventive procedures for HTLV-1 associated diseases.

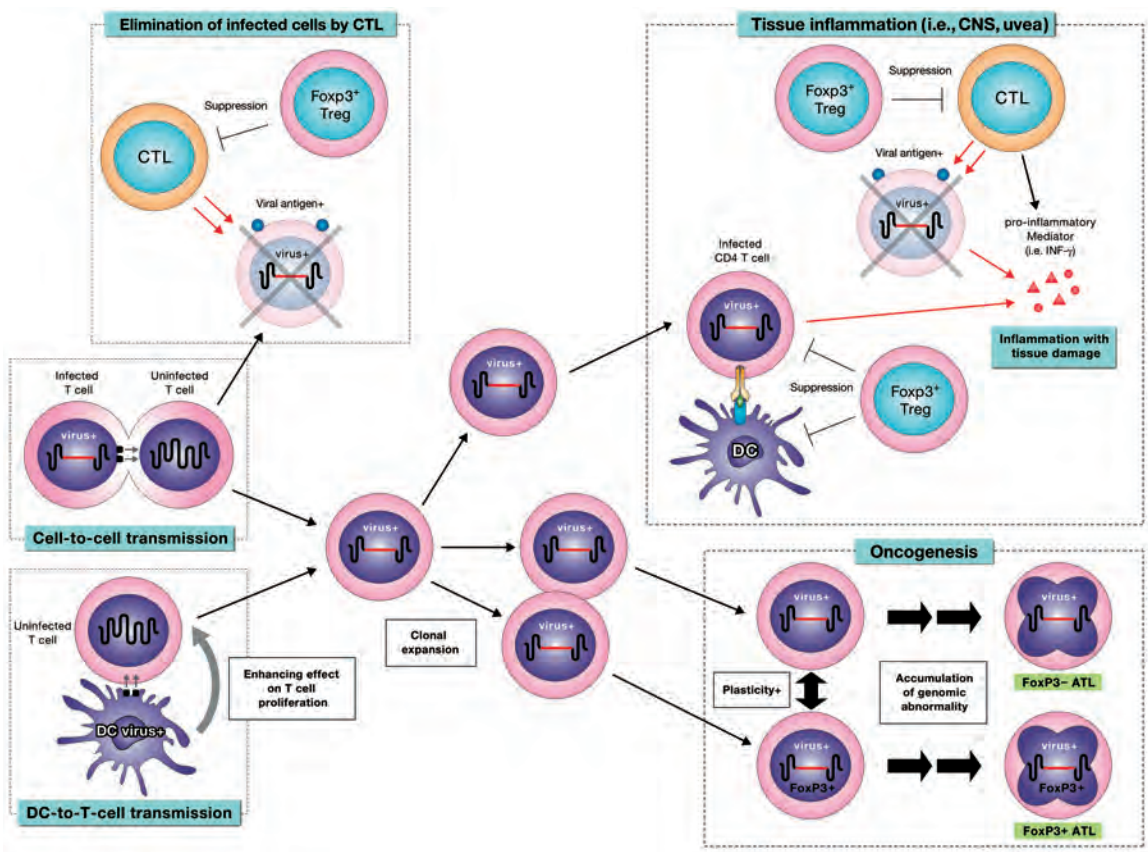

Fig. 4. The schematic figure of HTLV-1 infection in the host immune system. HTLV-1 enters and dysregulates the host immune system, resulting in chronic inflammation or transformation of infected cells. CTL, cytotoxic T cell ; DC, dendritic cell.

Antigen presenting cells (APCs) and T cell interaction

The most specialized machinery for T cells is obviously the T cell receptor and its signaling pathway. By using this system, naïve T cells recognize a cognate antigen, and then are activated either to differentiate or to undergo apoptosis. To understand the T-cell abnormalities induced by HTLV-1, we need to take into account APCs as crucial partners that regulate the fates of T cells *in vivo*. It is difficult for *in vitro* experiments to elucidate this aspect of HTLV-1 infection ; thus we need to establish useful *in vivo* systems of HTLV-1 infection. One of the most famous animal models is the tax transgenic mouse, which clearly demonstrated that tax potentially induces T-cell lymphoma[51,52] and chronic inflammatory diseases[53] *in vivo*, yet the process of the leukemogenesis and the detailed immunological status in that model still remain elusive. In addition, this transgenic system has a limitation in that we cannot study the immune response against the viral antigen. Several animal models, such as rabbits, rats, non-human primates, or humanized mice, can be infected with HTLV-1 and used as candidate hosts to study the effect of HTLV-1 on the interaction between T cells and APCs.[54]

Dendritic cells (DCs) are susceptible to HTLV-1 infection, and HTLV-1 infected DCs stimulate autologous lymphocyte proliferation of CD4 and CD8 T cells.[55,56] A recent study also clearly demonstrated that cell-free HTLV-1 efficiently infects DCs, and the infected DCs promote *de novo* infection of CD4 T cells (Fig. 4).[57] As with HIV, this transmission occurs in a biphasic manner. The early phase, called trans infection, occurs when DCs capture and transfer virions to CD4 T cells. The later phase, termed cis infection, occurs when virus produced *de novo* from infected DCs is transmitted to CD4 T cells. Cis infection should play a critical role in spreading the virus *in vivo*, because HTLV-1 is thought to be poorly infectious as a free virus and to spread primarily in a cell-to-cell manner. This study also indicated that the DC-T cell interaction induces activation of the T cells via the recognition of the antigen on the DCs. Thus the T cell's future differentiation status may be determined not only by the provirus within it, but by its interaction with the DC.

The cytotoxic T lymphocyte (CTL) response to HTLV-1

HTLV-1 is recognized as a foreign pathogen in infected individuals, and a virus-specific CTL response is found in the majority of carriers.[14,15] The CTL response is a critical component of the host immune response against HTLV-1. CTLs predominantly recognize the viral antigen Tax and contribute to the pathogenesis of chronic inflammatory diseases.[14,15] The level of CTL response differs among HTLV-1 carriers, and influences the 'set point' of proviral load. The frequency of HTLV-1 specific CTLs alone does not reflect the efficacy of the CTL response in chronically infected individuals, because antigenic stimulus fluctuates depending on the viral load.[58] If the immune response is efficient, the viral load decreases, which reduces the frequency of virus-specific CTLs. Rather, the overall lytic efficiency of the CTL population — which may reflect the frequency, specificity, and/or activation status of CTLs — must be evaluated by *ex vivo* culture of the CTLs together with HTLV-1-infected CD4 T cells from the same donor, and is well correlated with the proviral load.[59]

Since the genetic variation of HTLV-1 itself is quite limited, the level of CTL response must be determined by host factors. Virus-specific CTLs are activated via recognition of viral antigen presented on the APC. Since antigen presentation depends on HLA class I molecules, the HLA class I genotype influences the CTL response. Previous studies demonstrated that HLA-A02 and HLA Cw 08 are associated with low proviral load and low prevalence of HAM/TSP.[60,61]

Another factor that may influence the CTL response is the activity of $Foxp3^+$ T_{reg} cells. T_{reg} cells play a crucial role in controlling the CTL response through the direct suppression of APCs or CTLs via two mechanisms : one dependent on cell contact, i.e., CTLA-4, and another dependent on the secretion of inhibitory cytokines, such as TGF-β or IL-10.[62] There is a strong negative correlation between the frequency of CD4 $Foxp3^+$ Tax negative T_{reg} cells and the rate of CTL-mediated lysis of autologous HTLV-1 infected cells *ex vivo*.[63] This result suggests that T_{reg} cells indeed suppress the CTL response in HTLV-1 infected individuals.

A portion of CTLs are themselves infected with HTLV-1.[64] HTLV-1 specific CTLs are more susceptible to HTLV-1 infection compared with EBV-specific CTLs, indicating that cell contact between CTLs and APCs promotes the spread of HTLV-1 *in vivo* when HTLV-1 specific T cells encounter their antigens presented by APCs.

The CTL response is important not only for the understanding of the pathogenesis of inflammatory diseases but also for the treatment of ATL. An allogeneic bone marrow transplant,[65,66] which so far has been the only therapeutic procedure to achieve long term survival, increases the CTL response against the viral Tax antigen.[67] This observation suggests that enhancing the CTL response to viral antigens may be an effective therapeutic approach.

Concluding remarks

Since the identification of ATL as a distinct clinical entity, some progress has been made in preventing and treating the disease. In particular, the identification of a transmission route from the mother to her child through breast milk enables us to reduce *de novo* HTLV-1 infection.[68] In addition, recent approaches using allogeneic bone marrow transplantation have significantly improved the prognosis of ATL patients,[65,66] suggesting that enhancement of the immune response to HTLV-1

is a possible strategy for treatment of HTLV-1 associated human diseases. A better understanding of the interactions between HTLV-1 and the host immune system should provide us additional clues to effective therapies for HTLV-1-associated diseases.

REFERENCES

1 Van Dooren S, Salemi M, Vandamme AM : Dating the origin of the African human T-cell lymphotropic virus type-I (HTLV-I) subtypes. Mol Biol Evol 18 : 661-671, 2001

2 Takatsuki K : Discovery of adult T-cell leukemia. Retrovirology 2 : 16, 2005

3 Matsuoka M, Jeang KT : Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat Rev Cancer 7 : 270-280, 2007

4 Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, *et al.* : HTLV-I associated myelopathy, a new clinical entity. Lancet 1 : 1031-1032, 1986

5 Mochizuki M, Yamaguchi K, Takatsuki K, Watanabe T, Mori S, *et al.* : HTLV-I and uveitis. Lancet 339 : 1110, 1992

6 Nishioka K, Maruyama I, Sato K, Kitajima I, Nakajima Y, *et al.* : Chronic inflammatory arthropathy associated with HTLV-I. Lancet 1 : 441, 1989

7 Sugimoto M, Nakashima H, Watanabe S, Uyama E, Tanaka F, *et al.* : T-lymphocyte alveolitis in HTLV-I-associated myelopathy. Lancet 2 : 1220, 1987

8 Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, *et al.* : Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. Science 299 : 1713-1716, 2003

9 Koyanagi Y, Itoyama Y, Nakamura N, Takamatsu K, Kira J, *et al.* : *In vivo* infection of human T-cell leukemia virus type I in non-T cells. Virology 196 : 25-33, 1993

10 Etoh K, Tamiya S, Yamaguchi K, Okayama A, Tsubouchi H, *et al.* : Persistent clonal proliferation of human T-lymphotropic virus type I-infected cells *in vivo*. Cancer Res 57 : 4862-4867, 1997

11 Richardson JH, Edwards AJ, Cruickshank JK, Rudge P, Dalgleish AG : *In vivo* cellular tropism of human T-cell leukemia virus type 1. J Virol 64 : 5682-5687, 1990

12 Yoshida M : Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. Annu Rev Immunol 19 : 475-496, 2001

13 Jeang KT, Giam CZ, Majone F, Aboud M : Life, death, and tax : role of HTLV-I oncoprotein in genetic instability and cellular transformation. J Biol Chem 279 : 31991-31994, 2004

14 Jacobson S, Shida H, McFarlin DE, Fauci AS, Koenig S : Circulating $CD8^+$ cytotoxic T lymphocytes specific for HTLV-I pX in patients with HTLV-I associated neurological disease. Nature 348 : 245-248, 1990

15 Kannagi M, Harada S, Maruyama I, Inoko H, Igarashi H, *et al.* : Predominant recognition of human T cell leukemia virus type I (HTLV-I) pX gene products by human $CD8^+$ cytotoxic T cells directed against HTLV-I-infected cells. Int Immunol 3 : 761-767, 1991

16 Furukawa Y, Osame M, Kubota R, Tara M, Yoshida M : Human T-cell leukemia virus type-1 (HTLV-1) Tax is expressed at the same level in infected cells of HTLV-1-associated myelopathy or tropical spastic paraparesis patients as in asymptomatic carriers but at a lower level in adult T-cell leukemia cells. Blood 85 : 1865-1870, 1995

17 Gaudray G, Gachon F, Basbous J, Biard-Piechaczyk M, Devaux C, *et al.* : The complementary strand of the human T-cell leukemia virus type 1 RNA genome encodes a bZIP transcription factor that down-regulates viral transcription. J Virol 76 : 12813-12822, 2002

18 Cavanagh MH, Landry S, Audet B, Arpin-Andre C, Hivin P, *et al.* : HTLV-I antisense transcripts initiating in the 3'LTR are alternatively spliced and polyadenylated. Retrovirology 3 : 15, 2006

19 Murata K, Hayashibara T, Sugahara K, Uemura A, Yamaguchi T, *et al.* : A novel alternative splicing isoform of human T-cell leukemia virus type 1 bZIP factor (HBZ-SI) targets distinct subnuclear localization. J Virol 80 : 2495-2505, 2006

20 Satou Y, Yasunaga J, Yoshida M, Matsuoka M : HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. Proc Natl Acad Sci U S A 103 : 720-725, 2006

21 Usui T, Yanagihara K, Tsukasaki K, Murata K, Hasegawa H, *et al.* : Characteristic expression of HTLV-1 basic zipper factor (HBZ) transcripts in HTLV-1 provirus-positive cells. Retrovirology 5 : 34, 2008

22 Yoshida M, Satou Y, Yasunaga J, Fujisawa J, Matsuoka M : Transcriptional control of spliced and unspliced human T-cell leukemia virus type 1 bZIP factor (HBZ) gene. J Virol 82 : 9359-9368, 2008

23 Arnold J, Zimmerman B, Li M, Lairmore MD, Green PL : Human T-cell leukemia virus type-1 antisense-encoded gene, Hbz, promotes T-lymphocyte proliferation. Blood 112 : 3788-3797, 2008

24 Basbous J, Arpin C, Gaudray G, Piechaczyk M, Devaux C, *et al.* : The HBZ factor of human T-cell leukemia virus type I dimerizes with transcription factors JunB and c-Jun and modulates their transcriptional activity. J Biol Chem 278 : 43620-43627, 2003

25 Matsumoto J, Ohshima T, Isono O, Shimotohno K : HTLV-1 HBZ suppresses AP-1 activity by impairing both the DNA-binding ability and the stability of c-Jun protein. Oncogene 24 : 1001-1010, 2005

26 Zhao T, Yasunaga J, Satou Y, Nakao M, Takahashi M, *et al.* : Human T-cell leukemia virus type 1 bZIP factor selectively suppresses the classical pathway of NF-κB. Blood 113 : 2755-2764, 2009

27 Arnold J, Yamamoto B, Li M, Phipps AJ, Younis I, *et al.* : Enhancement of infectivity and persistence *in vivo* by HBZ, a natural antisense coded protein of HTLV-1. Blood 107 : 3976-3982, 2006

28 Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H : Adult T-cell leukemia : clinical and hematologic features of 16 cases. Blood 50 : 481-492, 1977

29 Hattori T, Uchiyama T, Toibana T, Takatsuki K, Uchino H : Surface phenotype of Japanese adult T-cell leukemia cells characterized by monoclonal antibodies. Blood 58 : 645-647, 1981
30 Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M : Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 155 : 1151-1164, 1995
31 Khattri R, Cox T, Yasayko SA, Ramsdell F : An essential role for Scurfin in $CD4^+CD25^+$ T regulatory cells. Nat Immunol 4 : 337-342, 2003
32 Hori S, Nomura T, Sakaguchi S : Control of regulatory T cell development by the transcription factor Foxp3. Science 299 : 1057-1061, 2003
33 Fontenot JD, Gavin MA, Rudensky AY : Foxp3 programs the development and function of $CD4^+CD25^+$ regulatory T cells. Nat Immunol 4 : 330-336, 2003
34 Kohno T, Yamada Y, Akamatsu N, Kamihira S, Imaizumi Y, *et al.* : Possible origin of adult T-cell leukemia/ lymphoma cells from human T lymphotropic virus type-1-infected regulatory T cells. Cancer Sci 96 : 527-533, 2005
35 Karube K, Ohshima K, Tsuchiya T, Yamaguchi T, Kawano R, *et al.* : Expression of FoxP3, a key molecule in $CD4^+CD25^+$ regulatory T cells, in adult T-cell leukaemia/ lymphoma cells. Br J Haematol 126 : 81-84, 2004
36 Karube K, Aoki R, Sugita Y, Yoshida S, Nomura Y, *et al.* : The relationship of FOXP3 expression and clinicopathological characteristics in adult T-cell leukemia/ lymphoma. Mod Pathol 21 : 617-625, 2008
37 Yano H, Ishida T, Inagaki A, Ishii T, Kusumoto S, *et al.* : Regulatory T-cell function of adult T-cell leukemia/lymphoma cells. Int J Cancer 120 : 2052-2057, 2007
38 Chen S, Ishii N, Ine S, Ikeda S, Fujimura T, *et al.* : Regulatory T cell-like activity of $Foxp3^+$ adult T cell leukemia cells. Int Immunol 18 : 269-277, 2006.
39 Shimauchi T, Kabashima K, Tokura Y : Adult T-cell leukemia/ lymphoma cells from blood and skin tumors express cytotoxic T lymphocyte-associated antigen-4 and Foxp3 but lack suppressor activity toward autologous $CD8^+$ T cells. Cancer Sci 99 : 98-106, 2008
40 Wang J, Ioan-Facsinay A, van der Voort EI, Huizinga TW, Toes RE : Transient expression of FOXP3 in human activated nonregulatory $CD4^+$ T cells. Eur J Immunol 37 : 129-138, 2007
41 Komatsu N, Mariotti-Ferrandiz ME, Wang Y, Malissen B, Waldmann H, *et al.* : Heterogeneity of natural $Foxp3^+$ T cells : a committed regulatory T-cell lineage and an uncommitted minor population retaining plasticity. Proc Natl Acad Sci U S A 106 : 1903-1908, 2009
42 Yamano Y, Takenouchi N, Li HC, Tomaru U, Yao K, *et al.* : Virus-induced dysfunction of $CD4^+CD25^+$ T cells in patients with HTLV-I-associated neuroimmunological disease. J Clin Invest 115 : 1361-1368, 2005
43 Yasunaga Ji, Sakai T, Nosaka K, Etoh Ki, Tamiya S, *et al.* : Impaired production of naive T lymphocytes in human T-cell leukemia virus type I-infected individuals : its implications in the immunodeficient state. Blood 97 : 3177-3183, 2001
44 Asquith B, Zhang Y, Mosley AJ, de Lara CM, Wallace DL, *et al.* : *In vivo* T lymphocyte dynamics in humans and the impact of human T-lymphotropic virus 1 infection. Proc Natl Acad Sci U S A 104 : 8035-8040, 2007
45 Gregersen PK, Olsson LM : Recent advances in the genetics of autoimmune disease. Annu Rev Immunol 27 : 363-391, 2009
46 Iwasaki Y, Ohara Y, Kobayashi I, Akizuki S : Infiltration of helper/inducer T lymphocytes heralds central nervous system damage in human T-cell leukemia virus infection. Am J Pathol 140 : 1003-1008, 1992
47 Kuroda Y, Matsui M : Cerebrospinal fluid interferon-gamma is increased in HTLV-I-associated myelopathy. J Neuroimmunol 42 : 223-226, 1993
48 Tendler CL, Greenberg SJ, Burton JD, Danielpour D, Kim SJ, *et al.* : Cytokine induction in HTLV-I associated myelopathy and adult T-cell leukemia : alternate molecular mechanisms underlying retroviral pathogenesis. J Cell Biochem 46 : 302-311, 1991
49 Yamano Y, Araya N, Sato T, Utsunomiya A, Azakami K, *et al.* : Abnormally high levels of virus-infected IFN-γ^+ $CCR4^+CD4^+$ $CD25^+$ T cells in a retrovirus-associated neuroinflammatory disorder. PLoS One 4 : e6517, 2009
50 Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, *et al.* : Functional delineation and differentiation dynamics of human $CD4^+$ T cells expressing the FoxP3 transcription factor. Immunity 30 : 899-911, 2009
51 Hasegawa H, Sawa H, Lewis MJ, Orba Y, Sheehy N, *et al.* : Thymus-derived leukemia-lymphoma in mice transgenic for the Tax gene of human T-lymphotropic virus type I. Nat Med 12 : 466-472, 2006
52 Ohsugi T, Kumasaka T, Okada S, Urano T : The Tax protein of HTLV-1 promotes oncogenesis in not only immature T cells but also mature T cells. Nat Med 13 : 527-528, 2007
53 Iwakura Y, Tosu M, Yoshida E, Takiguchi M, Sato K, *et al.* : Induction of inflammatory arthropathy resembling rheumatoid arthritis in mice transgenic for HTLV-I. Science 253 : 1026-1028, 1991
54 Lairmore MD, Silverman L, Ratner L : Animal models for human T-lymphotropic virus type 1 (HTLV-1) infection and transformation. Oncogene 24 : 6005-6015, 2005
55 Macatonia SE, Cruickshank JK, Rudge P, Knight SC : Dendritic cells from patients with tropical spastic paraparesis are infected with HTLV-1 and stimulate autologous lymphocyte proliferation. AIDS Res Hum Retroviruses 8 : 1699-1706, 1992
56 Makino M, Shimokubo S, Wakamatsu SI, Izumo S, Baba M : The role of human T-lymphotropic virus type 1 (HTLV-1)-infected dendritic cells in the development of HTLV-1-associated myelopathy/tropical spastic paraparesis. J Virol 73 : 4575-4581, 1999
57 Jones KS, Petrow-Sadowski C, Huang YK, Bertolette DC, Ruscetti FW : Cell-free HTLV-1 infects dendritic cells leading to transmission and transformation of $CD4^+$ T cells. Nat Med 14 :

429-436, 2008

58 Hanon E, Stinchcombe JC, Saito M, Asquith BE, Taylor GP, *et al.* : Fratricide among $CD8^+$ T lymphocytes naturally infected with human T cell lymphotropic virus type I. Immunity 13 : 657-664, 2000

59 Goon PK, Biancardi A, Fast N, Igakura T, Hanon E, *et al.* : Human T cell lymphotropic virus (HTLV) type-1-specific $CD8^+$ T cells : frequency and immunodominance hierarchy. J Infect Dis 189 : 2294-2298, 2004

60 Asquith B, Mosley AJ, Barfield A, Marshall SE, Heaps A, *et al.* : A functional $CD8^+$ cell assay reveals individual variation in $CD8^+$ cell antiviral efficacy and explains differences in human T-lymphotropic virus type 1 proviral load. J Gen Virol 86 : 1515-1523, 2005

61 Jeffery KJ, Usuku K, Hall SE, Matsumoto W, Taylor GP, *et al.* : HLA alleles determine human T-lymphotropic virus-I (HTLV-I) proviral load and the risk of HTLV-I-associated myelopathy. Proc Natl Acad Sci U S A 96 : 3848-3853, 1999

62 Jeffery KJ, Siddiqui AA, Bunce M, Lloyd AL, Vine AM, *et al.* : The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. J Immunol 165 : 7278-7284, 2000

63 Sakaguchi S, Yamaguchi T, Nomura T, Ono M : Regulatory T cells and immune tolerance. Cell 133 : 775-787, 2008

64 Toulza F, Heaps A, Tanaka Y, Taylor GP, Bangham CR : High frequency of $CD4^+FoxP3^+$ cells in HTLV-1 infection : inverse correlation with HTLV-1-specific CTL response. Blood 111 : 5047-5053, 2008

65 Utsunomiya A, Miyazaki Y, Takatsuka Y, Hanada S, Uozumi K, *et al.* : Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 27 : 15-20, 2001

66 Okamura J, Utsunomiya A, Tanosaki R, Uike N, Sonoda S, *et al.* : Allogeneic stem-cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/ lymphoma. Blood 105 : 4143-4145, 2005

67 Harashima N, Kurihara K, Utsunomiya A, Tanosaki R, Hanabuchi S, *et al.* : Graft-versus-Tax response in adult T-cell leukemia patients after hematopoietic stem cell transplantation. Cancer Res 64 : 391-399, 2004

68 Hino S, Katamine S, Kawase K, Miyamoto T, Doi H, *et al.* : Intervention of maternal transmission of HTLV-1 in Nagasaki, Japan. Leukemia 8 Suppl 1 : S68-70, 1994