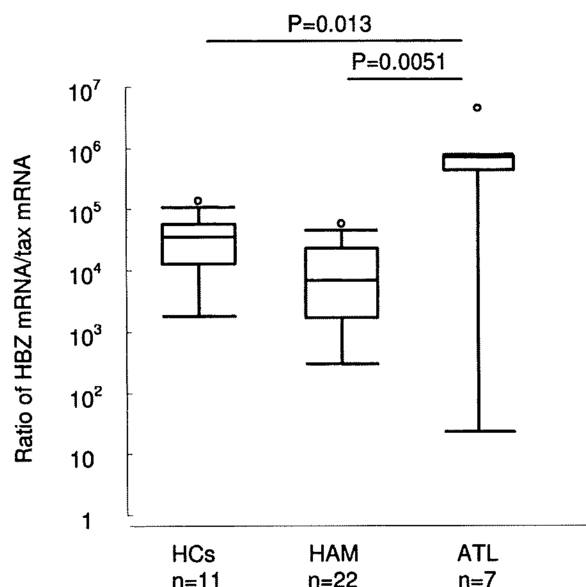

Figure 3
Comparison of HBZ mRNA load with tax mRNA load among HTLV-1 infected individuals in different clinical status. The ratio of HBZ mRNA/tax mRNA was significantly increased in ATL patients (median 700,512.24, range 23.11 – 4,308,413.02) than HAM/TSP patients (median 4,932.41, range 295.63–56,082.14) or HCs (median 35,602.96, range 1,804.77–137,999.33). The statistical differences between groups were calculated with a Mann Whitney U test.

HBZ mRNA load and HBZ mRNA/DNA ratio in PBMCs was decreased in HAM/TSP patients after effective IFN-treatment

Finally, to determine whether HTLV-1 mRNA load and mRNA/DNA ratio are associated with clinical improvement, we measured the HTLV-1 (both tax and HBZ) mRNA load and mRNA/DNA ratio before, during, and after interferon-alpha (IFN-α) treatment in four HAM/TSP patients who received 4 weeks of daily administration. Three million international units (IU) of IFN-α (human lymphoblastoid interferon-HLBI, Sumiferon® by Sumitomo Pharmaceutical Co., Osaka, Japan) were administrated per intramuscular injection. Two patients (HAM1 and 2) showed marked clinical improvement with the changes of the OMDS, whereas two patients (HAM3 and 4) did not show clinical improvement (without the changes of the OMDS) (Additional file 1). The HBZ mRNA load and mRNA/DNA ratio was decreased after IFN-α treatment in two patients who showed clinical improvement, whereas the HBZ mRNA load and mRNA/DNA ratio was stable during the treatment in two patients without clinical improvement (Additional file 1 and Figure 4). In contrast, the tax mRNA load and mRNA/DNA ratio did not show such a clear correlation with clinical improvement.

Discussion

In this study, we demonstrated that there was a statistically significant difference in the HTLV-1 HBZ mRNA load, but not tax mRNA load, in PBMCs between HAM/TSP patients and HCs. This is probably because tax mRNA was not expressed in significant numbers of individuals tested (60.7% of HAM/TSP patients, 34 out of 56; 71.1% of HCs, 27 out of 38; 30.0% of ATL patients, 3 out of 10), whereas HTLV-1 HBZ mRNA was expressed in all the infected individuals tested. There was also a statistically significant correlation between HTLV-1 HBZ mRNA load and HTLV-1 proviral load both in HAM/TSP patients and HCs, whereas tax mRNA load correlated with the HTLV-1 proviral load only in HCs but not in HAM/TSP patients. Recently, Usui et al. reported a similar observation [37]. Namely, HBZ spliced isoform mRNA was detectable in samples from most HCs and ATL patients, and was significantly correlated with the HTLV-1 proviral load. These results indicate that the regulation of HBZ mRNA expression is different from that of tax mRNA. It seems likely that HBZ mRNA is near-equally expressed by all provirus-positive cells despite different clinical status, while tax

Table 2: Results of rank correlation test between clinical and virological parameters.

	Proviral load		HBZ mRNA[a]		tax mRNA[b]		HBZ mRNA/DNA[c]		tax mRNA/DNA[d]	
	r	p	r	p	r	p	r	p	r	p
OMDS	0.169	0.285	0.328	**0.023**	0.241	0.401	0.252	0.091	0.257	0.300
Neopterin in CSF	0.512	**0.001**	0.437	**0.0052**	0.228	0.544	0.121	0.442	0.211	0.608
Serum Ab	0.117	0.431	0.185	0.194	0.234	0.333	0.102	0.497	0.248	0.279
CSF Ab	0.071	0.639	0.042	0.801	-0.0029	0.322	-0.046	0.690	0.0025	0.345

OMDS: Osame Motor Disability Scale for HAM/TSP
[a]HTLV-1 HBZ mRNA load = value of HBZ/value of HPRT
[b]HTLV-1 tax mRNA load = value of tax/value of HPRT
[c]HBZ mRNA/DNA ratio = HTLV-1 HBZ mRNA load/Proviral load
[d]tax mRNA/DNA ratio = HTLV-1 tax mRNA load/Proviral load

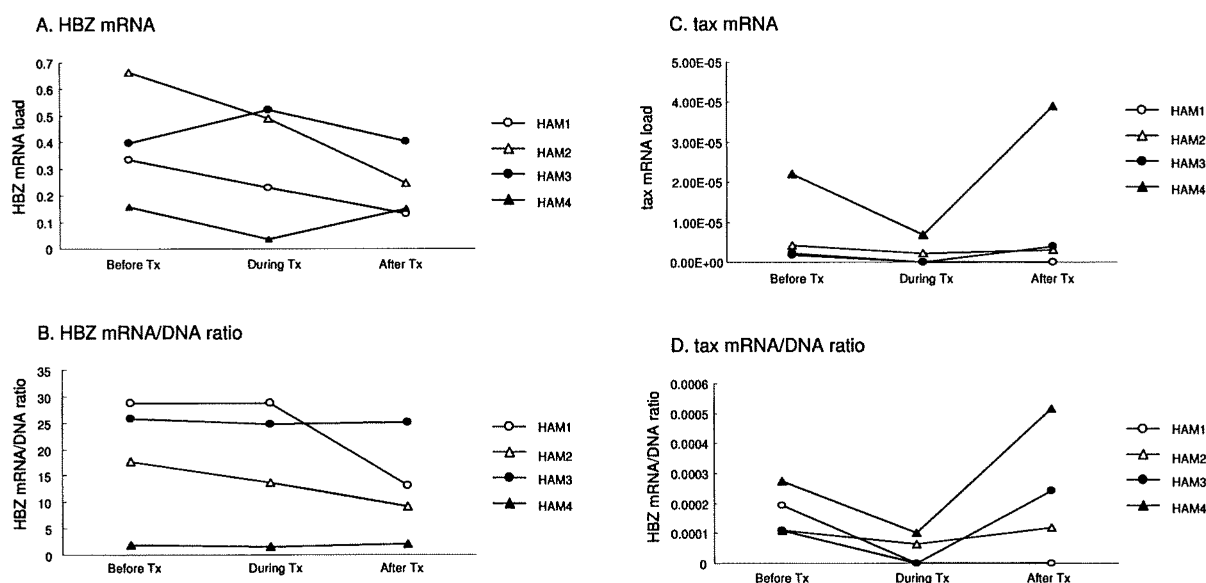

Figure 4
HBZ mRNA load and HBZ mRNA/DNA ratio in PBMCs were decreased in HAM/TSP patients after effective IFN-α treatment. To investigate whether HTLV-I mRNA load and mRNA/DNA ratio are associated with clinical improvement, we measured the HBZ mRNA/DNA ratio in four HAM/TSP patients who received 4 weeks of daily IFN-α administration (three million international units of IFN-α per one intramuscular injection). Two HAM/TSP patients with clinical improvement in Osame Motor Disability Score (OMDS) (HAM1 and 2) showed decreased HBZ mRNA load and HBZ mRNA/DNA ratio during the IFN-α treatment, whereas two HAM/TSP patients without clinical improvement in OMDS (HAM3 and 4) showed stable HBZ mRNA load and HBZ mRNA/DNA ratio during the IFN-α treatment. In contrast, the tax mRNA load and tax mRNA/DNA ratio did not show such a clear correlation with clinical improvement.

mRNA expression levels are variable in different clinical status.

When HTLV-1 tax or HBZ mRNA load was adjusted with HTLV-1 proviral DNA load (i.e. calculate mRNA/DNA ratio), the amount of tax and HBZ mRNA expressed per provirus was not significantly different between HAM/TSP patients and HCs, suggesting that the higher HTLV-1 proviral load seen in HAM/TSP patients caused higher HTLV-1 HBZ mRNA expression. This is consistent with our previous study using different methods for mRNA and DNA quantification [18], but differed from a previous American study using exactly the same methods, which showed significantly higher mRNA/DNA ratio in HAM/TSP patients than HCs [17]. In contrast to the previous study, which showed significant correlation between disease severity in HAM/TSP patients and both HTLV-1 tax mRNA load and mRNA/DNA ratio [17], we could not find such a correlation between clinical parameters of HAM/TSP patients including disease severity and both HTLV-1 tax mRNA load and mRNA/DNA ratio (Table 2). As we have already confirmed and reported the same levels of Tax protein expression in HTLV-1-infected PBMCs between HAM/TSP patients and HCs in the same cohort [50], the observed discrepancy may be due to the differences of a number of host genetic and virologic factors in HTLV-1 infected individuals, including differences in HLA haplotypes [51-53], differences in the amount of soluble suppressive factors and CD8+ T-cell responses, and differences in HTLV-1 tax genomic sequences [54]. As a recent report indicated that HTLV-I infection was associated with activated T-cell immunity in Jamaicans but with diminished T-cell immunity in Japanese persons [55], the interaction between different genes and/or environmental factors is also likely to contribute to the observed differences between the two populations. Namely, genetic resistance to infectious diseases that is formed by complex host genetic effects might be complicated further by pathogen diversity and environmental factors.

Another important observation is that the amount of HTLV-1 HBZ mRNA expression per provirus was more than a thousand times higher than tax mRNA expression both in HAM/TSP patients and HCs. Surprisingly, the amount of HTLV-1 HBZ mRNA expression per provirus was even higher in HTLV-1-infected PBMCs than in

infected cell lines, whereas tax mRNA expression was significantly higher in cell lines than infected PBMCs. Since HBZ suppresses Tax-mediated viral transcription [31], the abundant expression of HBZ mRNA in HTLV-1-infected PBMCs will be one of the molecular mechanisms involved in viral latency by suppressing HTLV-1 transcription and Tax expression, which may be a significant advantage to the virus in the infected cell by preventing its detection through a CTL response. Since we and others [37] found that down-regulation of tax mRNA (higher HBZ mRNA/tax mRNA ratio) was characteristic of primary ATL cells, imbalanced expression between HBZ and tax may induce the outgrowth of HTLV-1-transformed T cell and increase the risk of ATL, which is associated with a Tax-low or -negative phenotype.

We also found that the HTLV-1 HBZ mRNA load significantly correlated with the neopterin concentrations in CSF of HAM/TSP patients. Since neopterin levels in CSF have been used as an immunologic marker for monitoring disease activity and treatment efficacy of HAM/TSP [40,42,56], the quantitative analysis of HTLV-1 HBZ mRNA might also be used to monitor HAM/TSP disease activity. As expected, motor dysfunction of HAM/TSP patients evaluated by the OMDS score significantly correlated with HTLV-1 HBZ mRNA load ($P = 0.023$) but not with HTLV-1 tax mRNA load ($P = 0.401$). The correlation between HBZ mRNA load and two independent clinical parameters reflecting disease activities strongly suggest its stronger relevance than both tax mRNA and proviral load for HAM/TSP pathogenesis. This is further supported by the data that both HBZ mRNA load and HBZ mRNA/DNA ratio were decreased in HAM/TSP patients after effective IFN-α treatment. Collectively, our results suggest that higher HTLV-1 HBZ mRNA load may have relative prognostic value for the assessment of disease progression and could also be used as a surrogate marker to predict long-term outcome in HAM/TSP patients.

In summary, we showed that spliced HBZ gene was transcribed in all the HTLV-1 infected individuals examined, whereas tax mRNA was not transcribed in more than half in the same groups. Moreover, our data demonstrated a significant correlation between HTLV-1 HBZ mRNA load and HTLV-1 proviral load, neopterin concentrations in CSF and motor disability seen in HAM/TSP patients, indicating that HTLV-1 HBZ mRNA load may be a valid predictor of disease progression. Our present findings suggest that HTLV-1 HBZ mRNA expression plays a role not only in ATL, but also in the pathogenesis of the HTLV-1-associated inflammatory disease HAM/TSP.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MS designed and performed the experiments, analyzed the data, and wrote the paper; TM and KA provided clinical samples and assembled clinical database. YS and JY provided clinical samples and performed experiments. KS performed experiments, analyzed and interpreted data. MM made contribution to the conception and design of the study. YO contributed to obtaining funding and gave advice.

Additional material

Additional file 1

Changes in HBZ mRNA load and HBZ mRNA/DNA ratio in PBMCs of HAM/TSP patients after IFN- treatment.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1742-4690-6-19-S1.doc]

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Mini Review

Immunogenetics of human T-cell leukemia virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP)

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Human T-cell leukemia virus type 1 (HTLV-1) is a replication-competent human retrovirus associated with two distinct types of disease: the malignancy known as adult T-cell leukemia (ATL) and a chronic inflammatory central nervous system disease HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), whereas the vast majority of infected individuals remain asymptomatic carriers of the virus in lifetime. It is not yet fully understood why do certain individuals develop ATL or HAM/TSP, and how does HTLV-1 persist in spite of host immune response. This review focuses on the complex virus-host interactions and the cellular immune responses to HTLV-1 infection seen in HAM/TSP patients, which are important factors in determining HTLV-1 proviral load and the risk of developing disease.

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Key words HTLV-1, HAM/TSP, HLA, immune response, disease susceptibility

Introduction

Human T-cell leukemia virus type 1 (HTLV-1) infection is of particular interest to the field of immunology as well as microbiology because HTLV-1 is never be eliminated from the host in spite of a vigorous cellular and humoral immune responses against the virus, but causes no disease in vast majority of infected subjects (asymptomatic carriers: AC). Since HTLV-1 infection causes two distinct intractable diseases without effective treatment known as adult T-cell leukaemia[1,2] and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[3,4], evaluation of the individual risk for developing diseases in each AC would certainly be of considerable importance especially in HTLV-1 endemic area such as southern Japan, the Caribbean, Central and South America, the Middle East, Melanesia, and equatorial regions of Africa[5]. HAM/TSP is a chronic progressive myelopathy characterized by spastic paraparesis, sphincter dysfunction and mild sensory disturbance in the lower extremities, and the main pathological features are chronic inflamma-

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tion in the spinal cord characterized by perivascular lymphocytic cuffing and parenchymal lymphocytic infiltration. It is therefore widely assumed that the immune response against HTLV-1 causes the inflammatory spinal cord damage seen in HAM/TSP patients[6]. In this review, I shall summarize the recent work for HAM/TSP attempting to resolve outstanding question, i.e. why do some HTLV-1-infected people develop disease whereas the vast majority remains healthy in lifetime.

HTLV-1 infection and clinical features of HAM/TSP

HTLV-1 is classified as a complex retrovirus in the genus *Deltaretrovirus* of the subfamily *Orthoretrovirinae*, and infects 10-20 million people worldwide[7]. HTLV-1 can be transmitted through sexual contact[8], injection drug use[9], and breastfeeding from mother to child[10,11]. Although HTLV-1 infection is associated with a range of non-malignant chronic inflammatory diseases in the eyes, the lungs, or the skeletal muscles[7], HAM/TSP is the best-recognized with chronic progressive myelopathy characterized by spastic paraparesis, sphincter dysfunction and mild sensory disturbance in the lower extremities[12]. Pathological analysis of HAM/TSP autopsy materials indicates that the disease affects the spinal cord, predominantly at the thoracic level[13-15]. Loss of myelin and axons in the lateral, anterior, and posterior columns is associated with perivascular and parenchymal lymphocytic infiltration with the presence of foamy macrophages, proliferation of astrocytes, and fibrillary gliosis. Clinical progression of HAM/TSP is associated with increased proviral load in individual patients, and the ratio of proviral loads in cerebrospinal fluid (CSF) cells/in peripheral blood mononuclear cells (PBMCs) is significantly associated with clinically progressive disease[16]. MHC class I tetramer analysis of lymphocytes isolated from the CSF of HAM/TSP patients showed even higher frequencies of HTLV-1 Tax11-19-specific, HLA-A*02-restricted CD8 lymphocytes compared to PBMCs[17]. Therefore, an increased proliferation or migration of HTLV-1-infected and/or HTLV-1 specific lymphocytes to the central nervous system (CNS) might be closely associated with HAM/TSP pathogenesis[18]. The presence of atypical lymphocytes (so-called "flower-cells") in peripheral blood and CSF, a moderate pleocytosis and raised protein content in CSF are typically found in HAM/TSP patients. Oligoclonal bands, raised concentrations of inflammatory markers such as neopterin, tumor necrosis factor (TNF)-α, interleukin (IL)-6 and interferon (IFN)-γ, and an increased intrathecal antibody synthesis specific for HTLV-1 antigens have also been described[19].

Risk factors for HAM/TSP

Previous population association study of 202 cases of HAM/TSP and 243 AC in Kagoshima, HTLV-1 endemic southern Japan, revealed that one of the major risk factors is the HTLV-1 proviral load. The median proviral load was more than ten times higher in HAM/TSP patients than in AC, and a high proviral load was also associated with an increased risk of progression to disease[20]. It was suggested that genetic factors such as HLA is related to the high proviral load in HAM/TSP patients and genetic relatives. Namely, possession of the HLA-class I genes HLA-A*02 and Cw*08 was associated with a statistically significant reduction in both HTLV-1 proviral load and the risk of HAM/TSP, whereas possession of HLA-class I HLA-B*5401 and class II HLA-DRB1*0101 predispose to HAM/TSP in the same population[21,22]. Since the function of class I HLA proteins is to present antigenic peptides to cytotoxic T lymphocytes (CTL), these results imply that individuals with HLA-A*02 or HLA-Cw*08 mount a particularly efficient CTL response against HTLV-1, which may be an important determinant of HTLV-1 proviral load and the risk of HAM/TSP. Further analysis to look at non-HLA host genetic factors revealed that non-HLA gene polymorphism also affects the risk for developing HAM/TSP. For example, the TNF-α promoter -863 A allele[23] and the longer CA repeat alleles of MMP-9 promoter[24] predisposed to HAM/TSP, whereas IL-10 -592 A[25], SDF-1 +801A[23] and IL-15 +191 C alleles[23] conferred protection against HAM/TSP. The polymorphisms of MMP-9 and IL-10 promoter each linked to the HTLV-1-encoded transactivator Tax mediated transcriptional activity of each gene[24,25].

Meanwhile, although most studies of HTLV-1 genotype have reported no association between variants of HTLV-1 and the risk of HAM/TSP, Furukawa et al reported the association between HTLV-1 *tax* gene variation and the risk of HAM/TSP[26]. The *tax* subgroup A that belongs to cosmopolitan subtype A was more frequently observed in HAM/TSP patients and this effect was independent of protective allele HLA-A*02. HLA-A*02 appeared to give protection against only one of the two prevalent sequence variants of HTLV-1, *tax* subgroup B that belongs to cosmopolitan subtype B, but not against *tax* subgroup A in Japanese population[26]. Interestingly, HLA-A*02 appears not to give protection against infection with cosmopolitan subtype A in a population in Iran[27]. These findings suggest that both host genetic factors and HTLV-1 subgroup play a part in determining the risk of HAM/TSP, although the effect of HTLV-1 genotype is relatively small so the factors that determine the different outcomes of HTLV-1 infection must lie chiefly in the host.

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Estimation of the odds for developing HAM/TSP

Based on these observations, a best-fit logistic regression equation that can be used to predict the odds of HAM/TSP has been developed[23]. Using this equation, knowledge of HTLV-1-infected individuals' ages, sex, provirus load, HTLV-1 *tax* subgroup, and genotypes at the loci HLA-A (HLA-A*02), HLA-C (HLA-Cw*08), stromal cell-derived factor (SDF)-1 (+801G/A), and TNF-α (-863A/C) allowed for the correct identification of 88% cases of HAM/TSP in Kagoshima cohort. To validate whether this multivariate logistic equation can be useful to identify HAM/TSP related symptom in AC, the individual odds of 181 consecutive AC were calculated and compared with their clinical parameters and laboratory findings[28]. Interestingly, although no clear difference was seen between the odds of HAM/TSP and either sex, family history of HAM/TSP or ATL, and history of blood transfusion, however, brisk patellar deep tendon reflexes, which suggest latent central nervous system compromise, and flower cell-like abnormal lymphocytes, which is the morphological characteristic of ATL cells, has found to be associated with a higher odds of HAM/TSP. These observations indicated that this best-fit logistic regression equation may be useful for detecting subclinical abnormalities in AC in Kagoshima, where HTLV-1 endemic southern Japan.

The immune response to HTLV-1

1) The humoral immune response to HTLV-1

In HTLV-1 infection, anti-HTLV-1 antibody that often includes IgM is detected in all infected individuals, either AC or patients with HTLV-1-associated diseases. It has been reported that HAM/TSP patients generally had higher anti-HTLV-1 antibody titer than AC with the similar HTLV-1 proviral load[29-31]. These data suggest that there was persistent expression of HTLV-1 proteins *in vivo* and the existence of an augmented humoral immune response to HTLV-1 in HAM/TSP patients. Levin et al reported some intriguing evidence for antigen mimicry in HTLV-1 infection[32]. Namely, antibodies that recognize HTLV-1 Tax protein can cross-react with a host nuclear riboprotein hnRNP-A1. However, since the host protein hnRNP-A1 is not confined to the central nervous system but is widely expressed, and is not normally accessible to antibody attack, it is unlikely that anti-Tax antibody explains the onset or initial tissue damage of HAM/TSP. Rather, anti-Tax antibody might be associated with subsequent inflammation following initial tissue damage, which probably caused by the antiviral immune responses to HTLV-1 and induce the release of auto-antigens.

2) The natural killer (NK) cell response

Previous reports indicated that patients with HAM/TSP had both a lower frequency and a lower activity of NK cells (especially the $CD3^+$ $CD16^+$ subset) than AC, although the results were not normalized with respect to the proviral load[33]. Since an important mechanism of induction of NK cell-mediated killing is recognition by the NK cell of a complex of the non-polymorphic MHC molecule HLA-E bound to a peptide derived from the signal sequence of some other MHC class I molecules, synthetic tetramers of HLA-E with the HLA-G signal sequence peptide was used to identify NK cells in HAM/TSP patients[34]. The results clearly showed a lower frequency of HLA-E tetramer-binding cells in HAM/TSP patients than AC, and as in the earlier studies[33], this reduction in frequency was particularly notable in the $CD3^+$ cells whereas there was no significant difference in the frequency of HLA-E tetramer-binding $CD3^-$ cells between patients with HAM/TSP and AC. These results suggest that the activity of the NK or NK-like cell response was associated with the presence or absence of HAM/TSP. On the other hand, we previously reported that an uncontrolled preliminary trial by oral administration of viable *Lactobacillus casei* strain Shirota containing fermented milk for HAM/TSP patients resulted in significant increase of NK cell activity with improvements in clinical symptoms[35], suggesting that NK cells might be associated with the pathogenesis of HAM/TSP.

3) The regulatory T cells (Tregs)

It has been reported that HTLV-1 preferentially and persistently infects $CD4^+CD25^+$ lymphocytes *in vivo*[36], which contain the majority of the $Foxp3^+$ Tregs[37]. In HAM/TSP patients, the percentage of $Foxp3^+$ Tregs in $CD4^+CD25^+$ cells is lower than that in AC and uninfected healthy controls[38], however, the percentage of $Foxp3^+$ cells in the $CD4^+$ population tended to be higher in the HAM/TSP patients than in the AC[39]. This is probably because $CD25^+$ cells contain both Tregs and activated non-Tregs, and HTLV-1 infected individuals especially HAM/TSP patients increases the number of activated T cells expressing CD25. Interestingly, the percentage of $Foxp3^+$ Tregs positively correlated with the HTLV-1 proviral load and the CTL activity negatively correlated with the frequency of $Foxp3^+$ Tregs[39], suggesting that an increase in Tregs reduces CTL activity, which in turn increases the HTLV-1 proviral load.

4) The $CD4^+$ helper T cell response to HTLV-1

The HTLV-1 antigen most commonly recognized by $CD4^+$ T cells is the Envelope (Env) protein, in contrast with the

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immunodominance of Tax in the CD8+ T cell response. Since an HTLV-1 Env gp21 immunodominant epitope was restricted by HLA-DRB1*0101, and HLA-DRB1*0101 was associated with susceptibility to HAM/TSP in independent HTLV-1-infected populations in southern Japan[21,22] and northeastern Iran[27], a synthetic tetramer of DRB1*0101 and the immunodominant HTLV-1 Env380-394 peptide was used to analyze Env-specific CD4+ T cells directly *ex vivo*[40]. The results clearly showed that the frequency of tetramer+ CD4+ T cells was significantly higher in HAM/TSP patients than AC with similar proviral load. Direct *ex vivo* analysis of tetramer+ CD4+ T cells from two unrelated DRB1*0101 positive HAM/TSP patients indicated that certain TCR Vβs were utilized and antigen-specific amino acid motifs were identified in CDR3 regions from both patients. These data suggest that the observed increase in virus-specific CD4+ T cells in HAM/TSP patients, which may contribute to CD4+ T cell-mediated antiviral immune responses and to an increased risk of HAM/TSP, was not simply due to the rapidly growing HTLV-1 infected CD4+ T cells but was the result of *in vivo* selection by specific MHC-peptide complexes, as observed in freshly isolated HLA-A*0201/ Tax11-19 tetramer+ CD8+ T cells[41] and muscle infiltrating cells from HAM/TSP patients and HTLV-1 infected polymyositis patients[42].

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

Previous reports indicated that the HTLV-1 specific CD8+ CTL are typically abundant, chronically activated, and mainly targeted to the viral transactivator protein Tax[6]. Also, as already mentioned, the median proviral load in PBMCs of HAM/TSP patients was more than ten times higher than that in AC, and a high proviral load was also associated with an increased risk of progression to disease[20]. Furthermore, HLA-A*02 and HLA-Cw*08 genes were independently and significantly associated with a lower proviral load and a lower risk of HAM/TSP[21,22], and CD8+ T cells efficiently kill autologous Tax-expressing lymphocytes in fresh PBMCs in HTLV-1 infected individuals[43]. These data have raised the hypothesis that the class I-restricted CD8+ CTL response plays a critical part in limiting HTLV-1 replication *in vivo*, and that genetically determined differences in the efficiency of the CTL response to HTLV-1 account for the risk for developing HAM/TSP. However, since the frequency of HTLV-1-specific CD8+ T cells were significantly elevated in HAM/TSP patients than AC[44,45], and these cells have the potential to produce proinflammatory cytokines[46], there is a debate on the role of HTLV-1-specific-CD8+ T cells, i.e. whether these cells contribute to the inflammatory and demyelinating processes of HAM/TSP, or whether the dominant effect of such cells *in vivo* is protective against disease, although these two mechanisms are not mutually exclusive. Recently, we reported that a frequency of CD8+ T cells that were negative for costimulatory molecules such as CD27, CD28, CD80, CD86 and CD152 were significantly higher in patients with HAM/TSP than in age-matched uninfected controls, but there was no such difference between AC and uninfected controls[47]. We also found a significantly lower frequency of perforin+ cells and granzyme B+ cells in the CD8+ T cells in HTLV-1 infected subjects than in uninfected controls, although there was no significant difference between patients with HAM/TSP and AC. Furthermore, the lytic capacity of HTLV-1 specific CTL between HAM/TSP and AC estimated by CD107a mobilization assay showed the significantly lower CD107a staining in HTLV-1 specific CTL in HAM/TSP than AC. Based on these findings, we have suggested that patients with HAM/TSP have a high frequency of HTLV-1 specific CD8+ T cells with poor lytic capacity, whereas AC have a lower frequency of cells with high lytic capacity.

Conclusions

As shown in Figure 1, the evidence summarized in this paper is consistent with the idea that virus-host immunologic interactions play a pivotal role in HAM/TSP pathogenesis. Genetically determined less efficient CTL response against HTLV-1 may cause higher proviral load and antigen expression in infected individuals, which lead to activation and expansion of antigen-specific T cell responses, subsequent induction of large amounts of proinflammatory cytokines and chemokines, and progression of HAM/TSP development.

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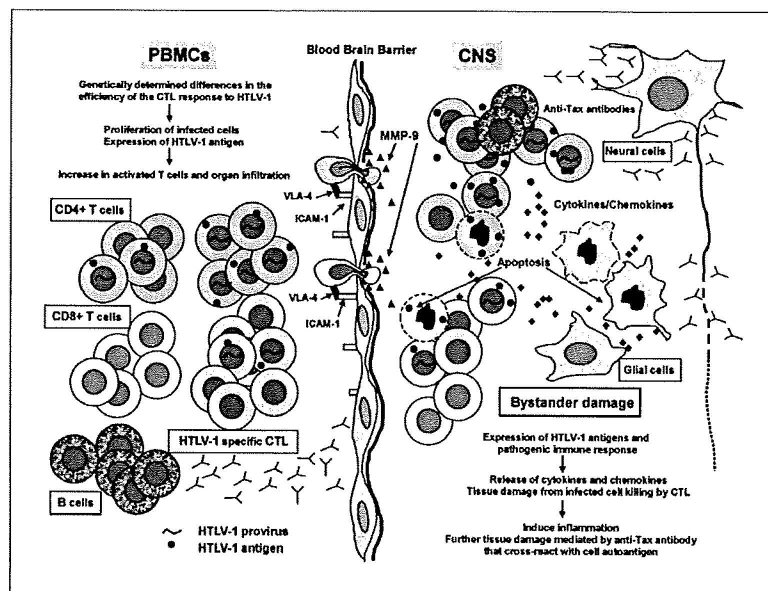

Fig.1 Hypothesis for the pathogenesis of Human T-cell leukemia virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP)

In patients with HAM/TSP, genetically determined less efficient CTL response against HTLV-1 may cause higher proviral load and antigen expression, which lead to activation and expansion of antigen-specific T cell responses, subsequent induction of large amounts of proinflammatory cytokines and chemokines, and progression of HAM/TSP development. It is also possible that the immunoglobulin G specific to HTLV-1-Tax, which cross-react with heterogeneous nuclear ribonuclear protein-A1 (hnRNP-A1), is associated with subsequent inflammation following initial tissue damage.

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