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.

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. 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), or sometimes leading to chronic inflammatory diseases such as HTLV-1 associated myelopathy/tropic spastic paraparesis (HAM/TSP), uveitis, arthritis, and alveolitis.

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 CD4 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. Although HTLV-1 can infect various kinds of cells, such as dendritic cells, B cells, macrophages, and T cells, the virus preferentially induces the clonal expansion of CD4 T cells. 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. Tax is a transcriptional co-factor, and hijacks many signaling pathways
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. 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, 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, and subsequently a novel splice isoform was identified by three different groups independently. 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. HBZ is reported to have an effect on the increased proliferation of infected cells. However, HBZ has been shown to suppress the transcriptional activity of c-Jun and the classical pathway of NF-κB in vitro, indicat-
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. On the other hand, HBZ RNA stimulates cell proliferation when over-expressed in vitro. 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, 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 CD4 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. 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 were derived from activated T cells. 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 (Treg cells) that function to suppress excessive immune responses. Within the CD4+CD25+ T cell subset, it was impossible to distinguish Treg cells from activated T cells until the identification of Foxp3 as a Treg "master switch." Several groups independently reported that Foxp3 plays crucial roles in the differentiation, function, and homeostasis of Treg cells. Most ATL cells are CD4+CD25+Foxp3+, indicating that they may be derived from Treg cells. The accumulation of Foxp3+ ATL cells could be a possible reason for the immune compromised status frequently observed in ATL cases, yet some ATL cells lost regulatory functions. As Foxp3 has important roles for Treg cell function, a report that Foxp3+ ATL cells had lower Foxp3 expression levels when compared with normal Foxp3+ Treg cells indicates that the suppressive function is impaired in such ATL cells. To further complicate the picture, the stimulation of naïve human CD4 T cells transiently induces the expression of Foxp3, indicating that the Foxp3+ ATL cells could possibly be derived from such an activated cell population. Conversely, a recent study indicated that Foxp3+ Treg cells lose plasticity: thus Foxp3+ Treg cells can convert to Foxp3 negative cells. This report indicates the possibility that Foxp3 negative ATL cells might come from Treg 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 Treg cells.

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. This indicates that Tax can influence the expression of Foxp3 in HTLV-1 infected Treg cells. These data collectively suggest that under-
standing Foxp3+ Treg 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 Treg 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, whereas HTLV-1 is enriched in CD4+CD45RO+ effector/memory CD4 T cells. 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, 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. Since CD4 T cells are the predominant cells detected in early inflammatory lesions, 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. Th1 cells, a major subset of CD4 T cells, are characterized by their ability to produce IFN-γ. In addition to Th1 cells, a recently identified Foxp3+ subset, CD4+CD45RA- Foxp3low non-Treg cells, also have the potential to produce various inflammatory cytokines, such as IFN-γ, IL-4, and IL-17. 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 lymphoma1,2,3 and chronic inflammatory diseases4,5 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.6

Dendritic cells (DCs) are susceptible to HTLV-1 infection, and HTLV-1 infected DCs stimulate autologous lymphocyte proliferation of CD4 and CD8 T cells.7,8 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).9 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.10,11 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.12,13 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.14 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.15

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.16,17

Another factor that may influence the CTL response is the activity of Foxp3+ Treg cells. Treg 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-10.18 There is a strong negative correlation between the frequency of CD4 Foxp3+ Treg cells and the rate of CTL-mediated lysis of autologous HTLV-1 infected cells ex vivo.19 This result suggests that Treg cells indeed suppress the CTL response in HTLV-1 infected individuals.

A portion of CTLs are themselves infected with HTLV-1,20 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,21,22 which so far has been the only therapeutic procedure to achieve long term survival, increases the CTL response against the viral Tax antigen.23 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.24 In addition, recent approaches using allogeneic bone marrow transplantation have significantly improved the prognosis of ATL patients.25,26 suggesting that enhancement of the immune response to HTLV-1
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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.

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