

# PTCL: Lessons from Adult T-cell Leukemia

Masao Matsuoka

*Institute for Virus Research, Kyoto University, Kyoto, Japan*

---

## Abstract

Peripheral T-cell lymphoma (PTCL) is a neoplastic disease of peripheral T-lymphocytes/NK cells, including PTCL unspecified, anaplastic large T-cell lymphoma (ALCL), IBL-like T-cell lymphoma (AILD), intestinal T-cell lymphoma (ITCL) and adult T-cell leukemia/lymphoma (ATL). The incidence of PTCL is relatively uncommon although its incidence shows significant variations in the geographical regions and racial populations. In Asia, its incidence is high due to HTLV-I infection in Japan. Molecular mechanisms of oncogenesis of PTCLs remain unknown. Therefore, analyses of ATL will give us a clue to clarify the molecular mechanism.

---

## 1. ATL

ATL was identified as an independent clinical entity in 1977 by Takatsuki et al., by its unique clinical features, and the clustering of patients in southwestern Japan. Thereafter, its causative agent, HTLV-I, was identified, which lead to the detailed characterization of ATL, and virological, epidemiological studies of HTLV-I associated diseases. HTLV-I was the first retrovirus that has been shown to be associated with human disease. The presence of provirus enables us to analyze the natural history from HTLV-I infection to onset of ATL. Such analyses could disclose the molecular mechanism of multi-step oncogenesis of ATL, and PTCL.

## 2. HTLV-I

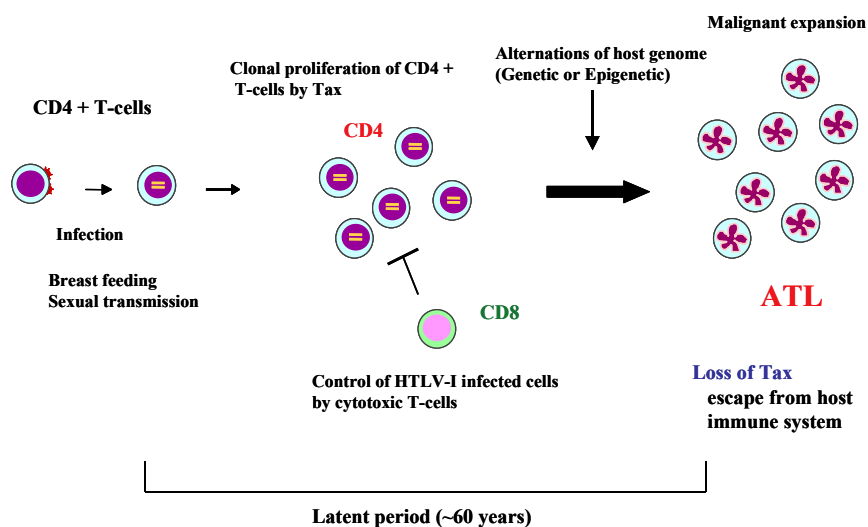
HTLV-I belongs to Oncovirinae subfamily of retroviruses, which includes the bovine leukemia virus (BLV), the human T-cell lymphotropic virus type II (HTLV-II), and the simian T-cell leukemia virus (STLV). Like other retroviruses, the HTLV-I proviral genome has *gag*, *pol* and *env* genes, flanked by long terminal repeat (LTR) sequences at both ends. A unique structure was found between *env* and the 3'-LTR, denoted the pX region, that encodes the regulatory proteins, p40<sup>tax</sup> (Tax), p27<sup>rex</sup> (Rex), p21, p12, and p13. Among them, Tax protein is thought to play a central role in the leukemogenesis of ATL, because of its pleiotropic actions. Tax does not bind to promoter or enhancer sequence by itself, but it interacts with cellular

proteins that are transcriptional factors or modulators of cellular functions. Tax can interact with IKK $\alpha$ , which causes phosphorylation of I $\kappa$ B and NF- $\kappa$ B activation, resulting in transcriptional activation of cellular genes such as interleukin 2, and interleukin 2 receptor genes. On the other hand, binding of Tax to CREB causes transcriptional activation of viral genes as well as cellular genes. Conversely, Tax can trans-repress the transcription of certain genes, such as *lck*, *p18* and DNA polymerase  $\beta$ . The direct interaction of Tax with cellular proteins can also interrupt their functions. Tax can inactivate the functions of p16<sup>INK4A</sup>, a key inhibitor of cyclin dependent kinases 4 and 6, MAD1, and p53.

Thus, the pleiotropic functions of Tax are thought to contribute to the immortalization of HTLV-I infected cells, especially CD4 positive T-lymphocytes. Indeed, the proliferation of HTLV-I infected cells in vivo has been shown to be clonal, as detected by analysis of integration sites. After infection with HTLV-I, a very long latent period, about 50 years in Japan, is present before the onset of ATL. Such a long latent period indicates that multi-step tumorigenesis is necessary for the development of ATL. During this latent period, genetic and epigenetic mutations are thought to accumulate in infected cells.

## 3. Natural History of HTLV-I Infection

Natural course of HTLV-I infection to ATL is thought to be as follows (Figure 1). HTLV-I transmission is mainly from mother-to-infant by breast-feeding or male-to-female by sexual intercourse. HTLV-I pro-



**Figure 1.** Natural history of HTLV-I infection. HTLV-I transmits from mother to child (breast feeding) or from male to female (sexual transmission). HTLV-I infected CD4 positive T-cells proliferated by the pleiotropic actions of Tax. During the latent period, the host immune system against HTLV-I was impaired, and the alternation of host genome accumulated, finally resulting in the onset of ATL. At late stage of leukemogenesis, tax gene was frequently inactivated, that enabled ATL cells to escape from the host immune system.

virus is detected mainly in CD4 positive memory T-lymphocytes in healthy carriers. Indeed, carriers with a high HTLV-I provirus load have an increased number of CD4 positive memory T-lymphocytes. This suggests that viral proteins, especially Tax, promote the proliferation of CD4 positive memory T-lymphocytes. HTLV-I provirus load, which is correlated with the number of HTLV-I infected cells, differed more than 100-fold among HTLV-I carriers. It was revealed that provirus loads fluctuated only 2- to 4-fold in most carriers, showing that provirus loads were relatively constant over time in individual carriers.

The HTLV-I provirus is genetically very stable, especially compared with HIV-1. It has been postulated that increased HTLV-I load is achieved not by replication of virus, but by clonal proliferation of infected cells. We showed that HTLV-I infected clones persisted over seven years in the same individuals. These persistent clones were CD4 positive lymphocytes, which is consistent with the fact that HTLV-I predominantly immortalizes CD4 positive T-lymphocytes in vitro.

#### 4. Molecular Mechanism of Leukemogenesis

A long latent period of about 50 years precedes the onset of ATL, suggesting the multistep mechanism of leukemogenesis (Figure 1). The *tax* gene in the aggressive forms of ATL was frequently inactivated by the somatic changes (mutation or deletion), and epigenetic changes, indicating that such ATL cells could not produce Tax, and did not need Tax protein for maintenance of leukemogenesis. This finding suggests that at the early stage of ATL, the expression of Tax play a

critical role that promotes the cell cycle and inhibits apoptosis of infected cells, however, at the late stage of leukemogenesis, acquired changes of host genome could replace the function of Tax. Since Tax is the major target of cytotoxic T-lymphocytes, loss of Tax protein enables ATL cells to escape from host immune surveillance. Although mutation of *p53* or deletion of *p16<sup>INK4A</sup>* gene were reported in ATL cases, their frequencies were about 10-20%, and such mutations were detected in the aggressive disease state. We showed the epigenetic change of *p16<sup>INK4A</sup>* gene according to the disease progression, suggesting that epigenetic changes contribute to leukemogenesis of ATL. To clarify the significance of epigenetic changes in the multi-step oncogenesis, we isolated hypermethylated DNA regions in ATL cells compared with genomic DNA from carrier state. Several genes have been shown to be silenced in ATL cells by DNA hypermethylation. Such genes were associated with cell cycle regulation or apoptosis. This study has revealed that multi-step mechanism of leukemogenesis mimics evolution. The cells with hypermethylation, that suppressed the expression of inhibitory genes for cell cycle or apoptosis, are thought to be selected during the leukemogenesis. This approach will clarify the new tumor-suppressor genes that play an important role in oncogenesis of ATL.

#### References

1. Matsuoka M. Adult T-cell leukemia/lymphoma. In *Infectious Causes of Cancer*, edited by Goedert JJ, Humana Press, Totowa, NJ, p.198-211, 2000.