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# Roles of HTLV-1 Tax in Leukemogenesis of Human T-Cells

Mariko Mizuguchi, Toshifumi Hara and Masataka Nakamura
*Human Gene Sciences Center, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Tokyo Japan*

## 1. Introduction

Human T-cell leukemia/lymphoma virus type 1 (HTLV-1), a member of the delta-retrovirus family, is an oncogenic retrovirus that is etiologically associated with adult T-cell leukemia (ATL) (Hinuma et al., 1981, Poiesz et al., 1980, Yoshida et al., 1982) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Gessain et al., 1985, Osame et al., 1986). ATL is characterized by an aggressive $CD4^+$ T-cell malignancy with resistance to anti-cancer therapeutics. It is currently estimated that HTLV-1 infects 10-20 million people in the world, endemically southwestern Japan, Africa, South America and the Caribbean basin (Proietti et al., 2005). HTLV-1 transmission mainly occurs from mother to child through breast milk followed by infection to child cells in a cell-cell contact manner (Kinoshita et al., 1987). Approximately 2-5% of HTLV-1-infected individuals develop ATL after a long latent period. The average Japanese ATL patients are 60 years old. Accumulation of genetic and epigenetic changes in provirus and host genes during the latent period is thought to be essential for immortalization and transformation of T-cells. However the pathogenesis of ATL by HTLV-1 remains incompletely understood.

Like other retroviruses, HTLV-1 provirus genome structure genes, gag, pro, pol, and env are flanked by 5′ and 3′ long terminal repeat (LTR). Besides the prototype genes, the HTLV-1 genome has the 1.6 kb pX region in the 3′ terminal region. The pX region codes for several non-structural molecules Tax1, Rex, p12, p13, p30, p21 and HBZ by combination of the reading frames and alternative splicing (Figure 1) (Nicot et al., 2005). Tax1 was initially identified as a trans-acting transcriptional activator of the HTLV-1 promoter in LTR, leading to virus replication (Fujisawa et al., 1985, Sodroski et al., 1984). Tax1 has the ability to modulate transcription of cellular genes through activation of at least three cellular transcriptional factors NF-κB, CREB/ATF and AP-1 (Yoshida, 2001). Tax1-mediated dysregulation of gene expression is believed to be implicated in cellular immortalization and transformation through multistep processes. Cell immortaliztion and transformation generally require at least three steps: cell growth promotion, prevention of apoptosis and escape from senescence. Involvement of Tax1 in three steps has been studies intensively and extensively; Introduction of the Tax1 gene induces phenotypic transformation in fibroblast cell lines (Tanaka et al., 1990), neoplastic transformation of primary rat fibroblast in co-operation with the ras oncogene, persistent interleukin (IL) 2-dependent growth of primary T-cells in vitro (Akagi et al., 1995, Grassmann et al., 1989), and development of tumors and

leukemia in mice (Grassmann et al., 1989, Nerenberg et al., 1987). Tax1 exertion may be important for the early stage of the development of ATL, because some ATL cells do not express Tax1. The disturbance of normal cellular environment by Tax1 may be an initial step of ATL development. This chapter focuses on recent advances in molecular basis of Tax1 implication in leukemogenesis.

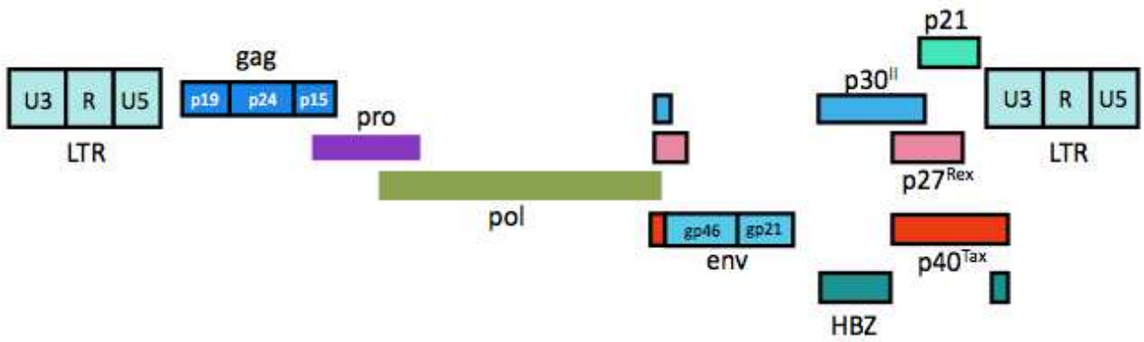


Fig. 1. Structure of HTLV-1 proviral genome

## 2. Effect of Tax1 on cell growth promotion

### 2.1 Cell cycle progression

Dysregulated cell cycle progression is potential for cellular transformation (Trimarchi and Lees, 2002). Cell growth is primarily controlled by the cell cycle, which in divided into five phases for convenience: the first gap (G1) phase, the DNA synthetic (S) phase, the second gap (G2) phase, the mitotic (M) phase and the resting (G0) phase. Mitogenic stimulation induces cell cycle progression by going through the restriction point between G1 and S phases (Trimarchi and Lees, 2002). Once they pass the restriction point, cells are destined to undergo one round of the cell cycle without further mitogenic stimulation. Most somatic cells usually stay at G0 or G1 phase. G1 cyclins and cyclin-dependent kinase (CDK) complexes (cyclin D1-CDK4, 6 and cyclin E-CDK2) control G1 to S transition (Dyson, 1998, Nevins, 1998, Trimarchi and Lees, 2002). Mitogenic stimulation activates cyclin-CDK complexes, which phosphorylates the retinoblastoma tumor suppressor protein (pRb), releasing active E2F that functions as a transcription factor to produce gene products required for G0/G1 to S transition (Figure 2).

Previous studies including our findings indicate that Tax1 is directly implicated in cell cycle control (Liang et al., 2002, Neuveut et al., 1998, Ohtani et al., 2000, Schmitt et al., 1998). Tax1 induces cell cycle progression from G0/G1 to S phases in normal peripheral blood lymphocytes (PBLs) and IL-2-dependent human T-cell line Kit 225 cells (Iwanaga et al., 2001, Ohtani et al., 2000). The advantage of Kit 225 cells is that their growth is arrested at the G1 phase by depletion of IL-2 without significant apoptosis, and growth promotion can be re-induced by the addition of IL-2 (Hori et al., 1987). Tax1 is known not to have the ability to bind directly to DNA elements and to perturb expression of a lot of cellular genes through interaction with cellular transcription factors NF-κB, CREB and AP-1 (Yoshida, 2001). Ectopic introduction of Tax1 into resting Kit 225 cells by recombinant adenoviruses revealed that a Tax1 mutant lacking the ability to activate NF-κB fails to cell cycle progression, suggesting that NF-κB is important for Tax1-mediated cell cycle progression (Iwanaga et al., 2001). To address the molecular mechanism underlying Tax1-induced cell cycle progression, effects of Tax1 on

expression of cell cycle regulators have been examined. Tax1 up-regulates expression of genes for cyclin D2, cyclin E, E2F1, CDK2, CDK4 and CDK6, while Tax1 reduced expression of genes for CDK inhibitors $p19^{INK4d}$ and $p27^{Kip1}$ in resting Kit 225 cells (Iwanaga et al., 2001, Ohtani et al., 2000). These results indicate that Tax1-dependent deregulation of cell cycle regulators is directly associated with abnormal cell cycle progression.

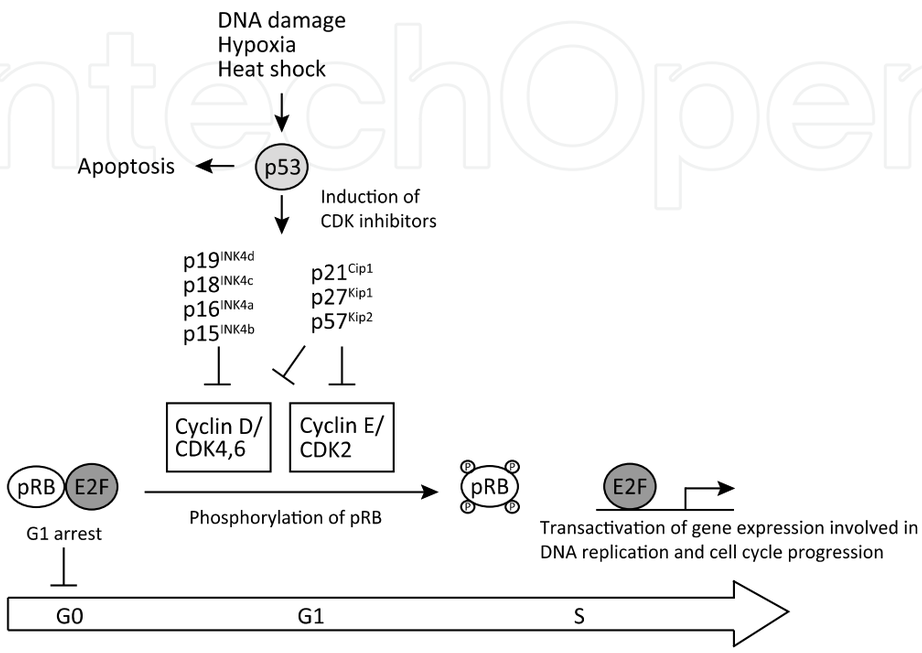


Fig. 2. Regulation of G1/S transition

### 2.2 Activation of E2F

E2F plays crucial roles in induction of the S phase by regulating expression of genes that encode a set of molecules involved in DNA replication and cell cycle progression (Figure 2) (Nevins et al., 1997). Thus it is important to understand how Tax1 affects E2F activity. Tax1-dependnt phosphorylation of pRb results in activation of E2F1 (Iwanaga et al., 2001). Active E2F1 enhances own transcription by direct interaction to the E2F promoter in Kit 225 cells, whereas the E2F gene promoter is not activated by Tax1 in rat embryonic fibroblast REF52 cells (Ohtani et al., 2000). This finding suggests that Tax1 induces a positive feedback loop of E2F in a cell lineage-dependent manner. Indeed Tax1 increases transcript levels of genes carrying the E2F binding sites in their promoters. The HsOrc1, DHFR, DNA polymerase α and Cdc6 gene are examples, all of which are necessary for DNA replication in S phase (Ohtani et al., 2000). The activity of Tax1 to activate NF-κB and/or NFAT is indispensable for E2F activation (Ohtani et al., 2000). Tax1 also trans-activated promoters with E2F sites of cell cycle regulatory genes such as c-myc, cyclin D2, cyclin E and cyclin A (Huang et al., 2001, Ohtani et al., 2000, Santiago et al., 1999). These results demonstrate that Tax1 induces cell cycle progression, partly by releasing active E2F molecules.

### 2.3 Interfere with mitosis

Surprisingly and interestingly, primary T-cells or Kit 225 cells transduced with Tax1 show the cellular G1/S entry, but proliferation of such cells is not observed (Iwanaga et al., 2001,

Ohtani et al., 2000), perhaps suggesting blockage of mitosis by Tax1. Similarly induction of Tax1 in PA18G-BHK-21 cells, which are Tax1-inducible syrian hamster kidney cell line, revealed cell cycle transition from G1 to S phase, but further progression to mitosis was not seen (Liang et al., 2002). In addition, Tax1-transduced cells show nuclear abnormalities and cytokinesis defects, which are similar to symptoms observed in ATL patients (Jin et al., 1998, Majone et al., 1993, Semmes and Jeang, 1996). However the exact roles of Tax1 in entire cell cycle progression will be elucidated by future studies.

## 3. Deregulation of cellular signaling by Tax1

### 3.1 Induction of cytokines and their receptors

Growth stimuli for T-cells are usually delivered by cytokines, in particular IL-2 acts as an effective growth factor for T-cells (Asao et al., 1994, Tanaka et al., 1994). Cytokines, which are expressed inducibly and transiently, bind to their specific receptors, transducing intracellular signalings important not only for cellular proliferation, but for differentiation and survival of lymphocytes (Rochman et al., 2009). Expression of cytokines is crucial for proliferation of lymphocytes. The α-chain of IL-2 receptor (IL-2Rα) is also induced by immune stimulation and its gene is the first identified cellular gene that is activated by Tax1 (Ballard et al., 1988, Ruben et al., 1988). Together with IL-2Rα, IL-2Rβ and the common γ-chain form the high affinity IL-2 receptor complex that is an actual growth signal transducer of T-cells (Takeshita et al., 1992). Furthermore, transient transfection studies showed that the IL-2 promoter is activated by Tax1 in an NF-AT and NF-κB pathway-dependent manner (Good et al., 1996, Hoyos et al., 1989, McGuire et al., 1993). These led to the hypothesis that Tax1 makes T-cells proliferative through autocrine and/or paracrine action of induced IL-2 and IL-2R. However recent studies revealed that Tax1-expressing T-cells do not produce either the IL-2 mRNA or protein (Akagi and Shimotohno, 1993, Chung et al., 2003). Hence, the IL-2/IL-2R autocrine loop mediated by Tax1 in transformation of T-cells has been reconsidered.

Tax1 trans-activates transcription of genes for other cytokines related to T-cell growth such as IL-9, IL-13, IL-15 and IL-21 (Azimi et al., 1998, Chen et al., 2008, Mizuguchi et al., 2009, Silbermann et al., 2008, Waldele et al., 2004). Notably, IL-21 is produced by activated $CD4^+$ T-cells and effectively promotes proliferation of T-cells in co-operation with IL-15 (Onoda et al., 2007, Parrish-Novak et al., 2000). IL-21 is similar to IL-2 and IL-15 in terms of biological activity and receptor constitution, which is composed of itself specific receptor(s) and the common γ-chain (Asao et al., 2001, Onoda et al., 2007, Parrish-Novak et al., 2000). The common γ-chain is a target of Tax1 at transcription (Ohbo et al., 1995). These observations suggest that incomplete progression of the cell cycle by Tax1 may be complemented by action of cytokines and their receptors induced by Tax1. Coordination between IL-21 and IL-15 induced by Tax1 may deliver more effective growth signals in T-cells. This notion does not exclude the possibility of implication of IL-2 in Tax1-mediated cell growth. IL-21 may function as a powerful inducer for T-cell growth in the presence of IL-2, which is released in immune responses to HTLV-1 infection.

### 3.2 Intracellular signaling

Cytokines deliver more effective growth signals in T-cells. Interaction of cytokines with their receptors activates Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and PI3 kinase growth signaling pathways (Kelly-Welch et al., 2003,

Marzec et al., 2008, Zeng et al., 2007). The JAK/STAT pathway is one of the major cytokine signaling pathways. JAK-mediated phosphorylation of receptor subunits increases phosphorylation and dimerization of STATs, resulting in activation of downstream genes essential for cell growth and immunity (Levy and Darnell, 2002). JAK and STAT proteins are unphosphorylated and inactive in normal quiescent lymphocytes. STAT3 and STAT5 in HTLV-1 infected T-cells are reported to be constitutively activated (Hall and Fujii, 2005, Migone et al., 1995). Persistent activation of STAT3 is shown to increase proliferation, survival, angiogenesis and metastasis in various human cancers (Yu et al., 2009). IL-21 preferentially activates STAT1 and STAT3, while IL-2 and IL-15 primarily activate STAT5 (Asao et al., 2001, Zeng et al., 2007). Co-operation of intrinsic cell cycle promotion with cytokine-dependent signal transduction may be essential for cell proliferation induced by Tax1.

The pathway involving phosphoinositide 3-kinase (PI3K) and its downstream kinase Akt provides cell survival and growth signals in T-cells (Cantley, 2002). PI3K primarily phosphorylates phosphatidylinositol-4,5-bisphosphate ($PIP_2$) to generate the second messenger, phosphatidylinositol-3,4,5-trisphosphate ($PIP_3$), which form a complex with Akt and phosphoinositide-dependent protein kinese 1 (PDK1) on the plasma membrane, where Akt is activated by phosphorylation by PDK1 and mTOR complex 2 (mTORC2) (Sarbassov et al., 2005). Active Akt phosphorylates several cellular proteins for cell survival and cell cycle entry. Tensin homolog deleted on chromosome 10 (PTEN) and Src homology 2 domain containing inositol polyphosphate phosphatase-1 (SHIP-1) inhibit the pathway by phosphorylation of $PIP_3$ (Cantley and Neel, 1999, Rohrschneider et al., 2000). The PI3K/Akt pathway is constitutively active in HTLV-1 transformed cells and ATL cells (Fukuda et al., 2005, Peloponese and Jeang, 2006). Tax1 induces the phosphorylation of Akt that is linked to NF-κB activation and p53 inhibition (Jeong et al., 2005). Inhibition of PI3K or Akt induces cell cycle arrest and apoptosis with accumulation of $p27^{Kip1}$ and caspase-9 activation in HTLV-1 transformed T-cells (Jeong et al., 2008). In addition, Tax1 down-regulates transcription for PTEN and SHIP-1 through NF-κB-mediated inhibition of the transcriptional coactivator p300 (Fukuda et al., 2009). These findings indicate that the PI3K/Akt pathway activated by Tax1 is involved in cell cycle progression and survive.

## 4. Modification of apoptosis by Tax1

Tax1 inactivates p53 (Tabakin-Fix et al., 2006). The transcription factor p53 is critical for prevention of abnormal cell proliferation. When DNA is damaged by γ radiation, ultraviolet and carcinostatic, cells express high amount of active p53, resulting in expression of genes essential for cell cycle arrest, DNA repair or apoptosis (Figure 2). The p53 gene is mutated in roughly 50% of various human cancers (Grassmann et al., 2005). Mutation of p53 is poorly defined in ATL cells. Tax1 neither binds p53 nor represses p53 gene expression. Two major findings have been reported regarding inactivation of p53 by Tax1. First, Tax1 and p53 competes with each other for binding to the coactivator CREB binding protein (CBP)/p300 and p53 loses the ability to activate transcription (Ariumi et al., 2000, Van Orden et al., 1999). Second, Tax1-mediated p53 inactivation is dependent on NF-κB activation. Tax1 facilitates the formation of functionally inactive complexes containing p65 (RelA) and p53, and this interaction requires p53 phosphorylation at serine-15, a site is preferentially phosphorylated in Tax1-expressing cells (Pise-Masison et al., 2000). Tax1-mediated interference with tumor suppressor p53 has been thought to facilitate resistance to apoptosis. Apoptosis is an

important mechanism with intrinsic active processes of programmed cell death, by which cells keep themselves from uncontrolled cell death. As p53 is one of pivotal molecules to trigger apoptosis, Tax1-mediated inactivation of p53 may predispose HTLV-1 infected cells to survive. In addition to Tax1-mediated inactivation of p53, Tax1 induces anti-apoptotic molecules such as Bcl-$\chi$L, XIAP and survivin (Tsukahara et al., 1999, Yoshida, 2001). In tumor cells, prevention of apoptosis is essential for their continuous growth. Anti-apoptotic effects of Tax1 may lead to cellular immortalization and contribute to accumulation of genetic mutations.

Conversely, perevious studies reported that Tax1 expression is closely linked to the induction of apoptosis (Chlichlia et al., 1995, Chlichlia et al., 1997, Kao et al., 2000). Tax1-mediated apoptosis occurs in Tax1-inducible cell line JPX-9 by activation of the Fas/FasL pathway (Chen et al., 1997). Tax1 has been reported to sensitize cells to apoptosis induced by DNA damaging agents. The results from human cDNA expression array analysis with HTLV-1 infected Tax1-expressing T-cells (C81) treated with $\gamma$ irradiation show up-regulation of various genes for cell cycle inducers and inhibitors, anti- and pro-apoptotic molecules (de la Fuente et al., 2003). Upon $\gamma$ irradiation, S and G2/M phase-enriched population increases in cell numbers with apoptosis, while little, if any, or no induction of apoptosis is associated with G0/G1 population (de la Fuente et al., 2003). The apparent paradox of the opposite effects of Tax1 on cell death remains to be elucidated. The choice between proliferation and cell death by Tax1 may be influenced by cell cycle state or intracellular status.

## 5. Immortalization by Tax1

Telomeres are DNA-protein complex structures located at the end of chromosomes (Blackburn, 1991). The structures are thought to contribute to the stabilization of linear chromosomes (Blackburn, 1991, Counter et al., 1992). Each cell division leads to the shortening of telomere length by the end-replication problem (Olovnikov, 1973, Watson, 1972). The shortening of telomeres results in chromosome instability, which is closely related to cellular senescence (Allsopp et al., 1992). Thus most human somatic cells have a limited replicative life span due to shortening of the telomere length. To avoid telomere shortening, transformed cells and germline cells appear to have certain compensatory mechanisms (Counter et al., 1994, Kim et al., 1994). One mechanism synthesizing terminal telomere sequences is mediated by the reibonucleoprotein enzyme telomerase, whose activity is restricted by expression of its catalytic subunit human telomerase reverse transcriptase (hTERT) (Meyerson et al., 1997, Nakamura et al., 1997). Development and maintenance of ATL probably require telomerase activity and indeed ATL cells carry telomerase activity (Uchida et al., 1999). Therefore activation of telomerase seems to be one of key events in development of ATL.

Effects of Tax1 on expression of telomerase in human T-cells remains controversial. An early report concerning this issue suggested that Tax1 reduced telomerase activity in human T-cell line Jurkat cells and Tax1 negatively regulated hTERT promoter activity (Gabet et al., 2003). In contrast, other group showed that Tax1 stimulated the endogenous hTERT promoter through NF-$\kappa$B activation (Sinha-Datta et al., 2004). Recent studies may provide systemic solution to the discrepancy. Tax1 activates hTERT gene expression only in resting T-cells, while hTERT expression is not significantly changed by Tax1 in growing cells (Hara et al., 2008). Thus, the cell cycle state may differentially influence action of Tax1 on hTERT expression in human T-cells. The activity of Tax1 to promote cell cycle progression may be critically linked to regulation of expression of the hTERT gene, because kinetics of Tax1-mediated activation of

the hTERT promoter parallels Tax1-mediated cell cycle progression (Matsumura-Arioka et al., 2005). In leukemia cells, Tax1 may be negatively associated with or independent of regulation of hTERT expression, rather epigenetic changes in the promoter in leukemia cells may significantly contribute to constitutive activation of the hTERT promoter. It may be important that strict repression of telomerase expression in normal T-cells to avoid undesirable immune responses and malignant transformation. An element involved in repression in the promoter is suggested (Gabet et al., 2003, Hara et al., 2008).

## 6. HTLV-1 Tax and HTLV-2 Tax

HTLV-2 is close to HTLV-1 in genetic and biological terms, showing ~70% sequence homology with each other (Feuer and Green, 2005). HTLV-2 encodes Tax2, which shows ~75% sequence homology to Tax1 (Feuer and Green, 2005). Tax1 and Tax2 have been shown to important roles in immortalization of T-cells in an IL-2 dependent manner, though HTLV-2 has not been linked with development of hematological malignant diseases (Feuer and Green, 2005). Differences in functional domains between Tax1 and Tax2 has been demonstrated. Tax1 possesses a leucine zipper like region (LZR) within amino acids 225-232 and the PDZ binding motif (PBM) at C-terminus, which are responsible for Tax1-mediated p100 processing and p52 nuclear translocation (Higuchi et al., 2007, Shoji et al., 2009).

The NF-κB pathway is tightly controlled in normal T-cells, and transiently activated upon immune stimulation. On the other hand, aberrant NF-κB activation is implicated in many types of cancer, especially hematological malignancies such as leukemia, lymphoma and myeloma (Karin, 2006). In HTLV-1 infected T-cells, NF-κB is constitutively activated, which is also thought to be linked to immortalization of T-cell by HTLV-1 and HTLV-2 (Mori et al., 1999, Robek and Ratner, 1999, Ross et al., 2000). Tax1 activates both the canonical (mainly consisting of the p50 and p65 subunits) and non-canonical (mainly consisting of the p52 and RelB subunits) NF-κB pathways. These are consequences of interaction of Tax1 with IKK complex. In contrast, although Tax2 can activate the canonical pathway to a level comparable to Tax1, Tax2 rarely induces the p100 processing because of lacking the LZR and PBM regions (Higuchi et al., 2007, Shoji et al., 2009).

Recent studies demonstrate that Tax2 induces expression of IL-2, but Tax1 fails to induce IL-2 production (Figure 3) (Niinuma et al., 2005). This finding prompted us to search for

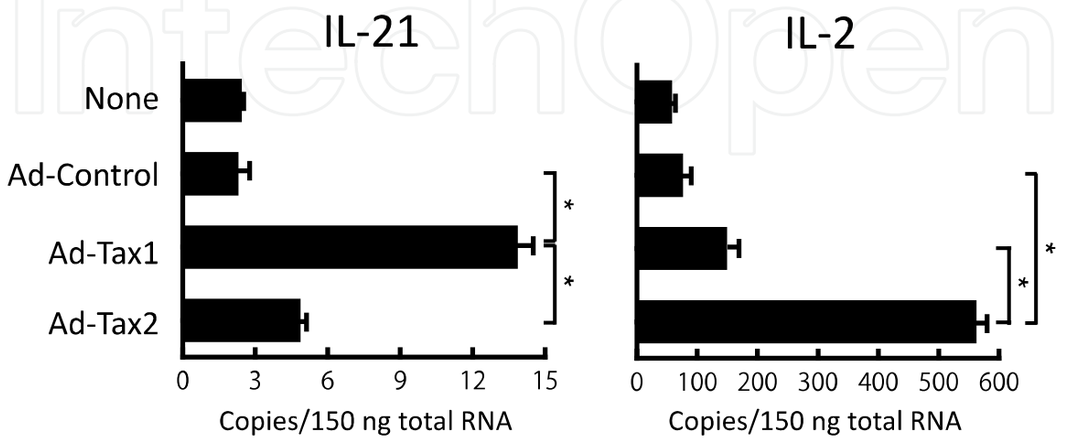


Fig. 3. Differential cytokine expression by Tax

another factor(s), which is differently induced between Tax1 and Tax2. In contrast to IL-2 induction, Tax1 induced IL-21 expression in $CD4^+$ T-cells, but Tax2 did not (Figure 3) (Miuguchi et al., 2009). The IL-21 promoter NF-κB binding site is activated by the p52/RelB complex by direct binding in a Tax1-dependent manner, probably reflecting the difference in NF-κB activation between Tax1 and Tax2. The functional differences between Tax1 and Tax2 causes different profiles of cytokine production, and may be related to phathogenesis between HTLV-1 and HTLV-2.

## 7. Conclusion

HTLV-1 is the first human retrovirus, which causes leukemia/lymphoma. Before the discovery of HTLV-1, many oncogenic retroviruses have been found, which induce malignant tumors in animals such as avian and rodent (Maeda et al., 2008). Most animal oncogenic retroviruses carry oncogenes, but they are totally different from the HTLV-1 oncogene for Tax1. Oncogenes, called v-onc, in animal retroviruses are usually derived from host cells, while Tax1 has no identity in host cells in terms of the origin of oncogene. Action of oncogenes are also different, unlikely to animal oncogenes, whose products are directly integrated cellular signaling pathways with dysregulated activities, Tax1 acts as transcriptional modulator that indirectly affects transcription of cellular genes related to immortalization and transformation. Therefore literature studies concerning animal retrovirus oncogenes was not much helpful in analyzes of mode of action of Tax1 in leukemogenesis.

Tax1 is a molecule of HTLV-1 products that shows strong immunogenicity (Kannagi et al., 1991). Human $CD8^+$ T-cells target Tax1-expressing cells. It is probably expected that most Tax1-expressing cells are killed by this mechanism. Thus Tax1 functions as a molecule both advantageous and disadvantageous to virus survive in vivo. Only cells escaped from immune attack further require genetic and epigenetic changes to become full transformants. These are may be reasons why ATL occurs after the long latent period at low frequency. In summary, Tax1 provides cells abilities of cell growth promotion, apoptosis prevention and senescence avoidance, but Tax1 alone may be insufficient for ATL development.

## 8. Acknowledgements

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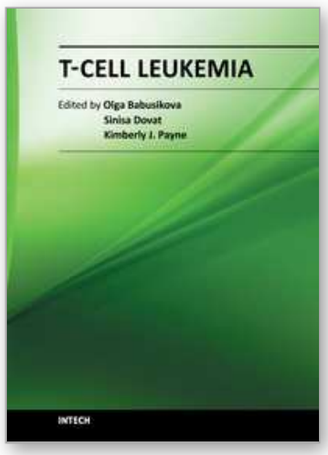


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The purpose of this book is to provide a comprehensive review of the scientific advances in T-cell malignancies and to highlight the most relevant findings that will help the reader understand both basic mechanisms of the disease and future directions that are likely to lead to novel therapies. In order to assure a thorough approach to these problems, contributors include basic scientists, translational researchers and clinicians who are experts in this field. Thus, the target audience for this book includes both basic scientists who will use this book as a review of the advances in our fundamental knowledge of the molecular mechanisms of T-cell malignancies, as well as clinicians who will use this book as a tool to understand rationales for the development of novel treatments for these diseases.



**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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