Acta Medica et Biologica
Vol. 47, No.3, 85-96, 1999

Activation of Nuclear Factor-κB/Rel Proteins by Human T-Cell Leukemia Virus Type I

Naoki MORI,[1] Naoki YAMAMOTO[1] and Masahiro FUJII[2]

[1]Department of Preventive Medicine and AIDS Research, Institute of Tropical Medicine, Nagasaki University, Nagasaki and [2]Department of Virology, Niigata University School of Medicine, Niigata, Japan

Received April 15 1999

Summary. **Human T-Cell leukemia virus type I (HTLV-I) is a human retrovirus that is associated with the development of adult T-cell leukemia (ATL) and HTLV-I-associated myelopathy/tropical spastic paraparesis. The 40 kDa viral protein Tax is thought to play a critical role in the development of these diseases since it transforms human T lymphocytes *in vitro*, and induces various types of tumors in transgenic animals carrying *tax* gene. Tax was originally identified as the transcriptional activator of its own viral promoter in a long terminal repeat. Thereafter, Tax has been shown to dysregulate cellular growth control mechanisms by affecting the transcription of cellular genes. Tax does not bind directly to DNA, but instead interacts with cellular factors to modulate their activities. Host transcription factors whose activity is modulated by Tax include nuclear factor (NF)-κB/Rel. NF-κB/Rel transcription factors participate in the activation of numerous genes involved in immune regulation/inflammation as well as cellular growth control including genes encoding cytokines, cell surface receptors, adhesion molecules, and acute phase proteins. This article reviews the molecular mechanisms of Tax that affect NF-κB/Rel activity and the role of NF-κB/Rel in the regulation of celular genes expression as well as cellular transformation by HTLV-I. In addition, we present a possible alternative mechanism involved in the Tax-independent activation of NF-κB/Rel in ATL cells *in vivo*, which might be involved in the late stages of leukemogenesis.**

Key words—HTLV-I, ATL, Tax, NF-κB/Rel, IκB.

Correspondence: Naoki Mori M.D., Department of Preventive Medicine and AIDS Research, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan.

Introduction

Human T-cell leukemia virus type I (HTLV-I) was initially discovered as a causative agent of a hematopoietic malignancy, adult T-cell leukemia (ATL).[1-3] Subsequent studies implicated HTLV-I in the pathogenesis of a variety of diseases such as HTLV-I-associated myelopathy/tropical spastic paraparesis,[4,5] uveitis,[6] arthropathy,[7] Sjögren's syndrome,[8] dermatitis,[9] and myositis.[10]

HTLV-I is a retrovirus, and transforms primary human T cells *in vitro*. Unlike most animal oncogenic retroviruses, HTLV-I neither encodes a known oncogene homologous to cellular gene[11] nor activates endogenous proto-oncogenes by site-specific integration of the provirus.[12] Instead, HTLV-I has a transforming gene *tax*, the product of which likely plays a central role in the development of the ATL. For instance, Tax transforms rodent fibroblast cell lines and primary T cells *in vitro*.[13-15] Transgenic mice expressing Tax develop mesenchymal tumors and large granular lymphocytic leukemia.[16-18]

Tax is a potent transcriptional activator of the HTLV-I long terminal repeat (LTR) as well as several cellular genes (Fig. 1). For example, Tax upregulates the expression of cellular genes, such as cytokine growth factors [e.g., interleukin (IL)-2, IL-6, and granulocyte-macrophage colony-stimulating factor], their receptors [e.g., the α chain of IL-2 receptor (IL-2Rα)], proto-oncogenes (e.g., c-*fos*, c-*jun*, and c-*myc*), transcription factors (e.g., egr-1 and egr-2), and adhesion molecules (e.g., ICAM-1 and VCAM-1).[19-27] Tax can also repress the expression of several genes including the DNA repair enzyme (β-polymerase), tumor suppressor genes (NF-1 and p53),

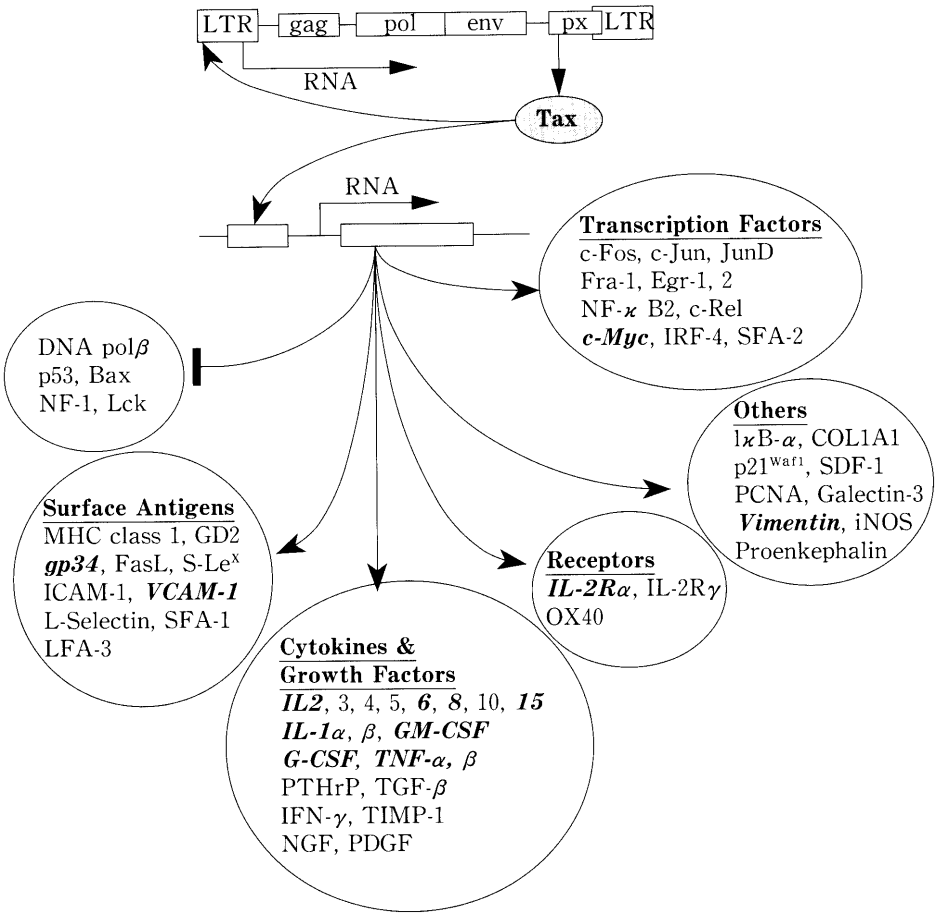

Fig. 1. Cellular genes activated by the HTLV-I transactivator protein, Tax. NF-κB proteins are involved in the transactivation of several cellular genes (*italic*).

and anti-apoptotic gene (Bax).[28–32] The aberrant regulation of these cellular genes by Tax has been implicated in the transformation of T cells by HTLV-I.

Tax does not directly bind to the enhancer DNA of the cellular genes but instead activates the transcription by modulating the activities of various host transcription factors, e. g., serum response factor (SRF), cyclic AMP response element binding protein/activating transcription factor (CREB/ATF), and nuclear factor (NF)-κB. In addition, recent studies have shown that the basic helix-loop-helix family of cellular transcription factors mediates the repression of cellular genes by Tax.[28,30,32] Tax also interacts directly with components of the basal transcription complex such as the TATA-binding protein[33] or with transcriptional coactivators such as the CREB-binding protein which mediate interactions between CREB and the basal transcriptional complex.[34] Thus, Tax can act as a bridging factor between transcription factors and the basal transcription complex, thereby stimulating transcription. Another mechanism for the activation of transcription involves Tax-induced increase in DNA binding by enhancing the dimerization of several transcription factors.[35–37]

Recently, Tax was shown to exhibit another function unrelated to its role as a transcriptional modulator. Tax binds to $p16^{INK4A}$, an inhibitor of cyclin-dependent kinases Cdk4 and Cdk6.[38] These Cdks are essential for the control of G_1-phase progression. Thus, Tax may activate Cdks by pulling off INK4 inhibitors like $p16^{INK4A}$ and promote the cell cycle in HTLV-I-infected lymphocytes.

Tax has the capacity to constitutively activate the NF-κB/Rel family of transcription factors,[19] thereby activating a set of NF-κB-responsive cellular genes that are normally transcribed in response to T cell activation signals. These genes include those encoding the growth factor IL-2 and IL-2Rα.[19,22] The mechanism of NF-κB activation by Tax is different

from those of other transcription factors, and has been the subject of intense investigation. This review focuses on the activation of NF-κB by Tax, which is associated with the transformation of primary T cells by HTLV-I *in vitro* as well as the leukemogenesis of HTLV-I *in vivo*.

1. Activation of NF-κB by HTLV-I Tax

Mechanisms of activation of NF-κB

NF-κB is a family of transcription factors, and the prototype NF-κB complex corresponds to a heterodimer of p50 (*NFKB1*) and RelA (p65).[39-41] Other family members include RelB, c-Rel, p52 (*NFKB2*). All family members have a Rel homology domain which mediates the dimerization and DNA binding in a sequence specific manner. Prior to activation, NF-κB exists in an inactive state in cells and is sequestered in the cytoplasm by physically interacting with a set of inhibitor proteins, IκBs (IκBα, IκBβ, IκBγ, and IκB/ε), p105 (*NFKB1*) , and p100 (*NFKB2*).[39-41] These inhibitor proteins all have ankyrin-repeats that mediate the interaction with NF-κB/Rel proteins. Stimulation with proinflammatory cytokines [e.g., tumor necrosis factor (TNF)-α and IL-1], phorbol myristate acetate (PMA), lipopolysaccharide (LPS), growth factors (e. g., IL-2), and others leads to the phosphorylation of IκBs such as IκBα on two serine residues located at positions 32 and 36. This modification of IκBα targets its rapid ubiquitousness and degradation within the 26S proteasome. The degradataion of cytoplasmic IκBα allows the nuclear translocation of NF-κB.[39-41] p105 and p100 have a Rel homology domain at the N-terminus and ankyrin-repeats at the C-terminus, and act as a precursor of p50 and p52 NF-κB/Rel, respectively. Similar to IκBs, p105 is also degraded in the proteasome,[42] but the degradation is incomplete and yields p50.

Kinetics of NF-κB activation by Tax

The activation of NF-κB/Rel by Tax is characterized by a pronounced increase in the nuclear accumulation of NF-κB/Rel complexes. These complexes include p50 or p52 heterodimers with RelA and/or c-Rel. There are two phases in the Tax-mediated generation of nuclear NF-κB/Rel complexes.[43] Kinetics analysis using a T-cell line carrying inducible *tax* gene has shown that Tax initially promotes the nuclear accumulation of p50/RelA, followed by that of p50/c-Rel or p52/c-Rel. The initial increase of p50/RelA by Tax is a posttranslational event, since the levels of mRNA and protein of these subunits are not affected. On the other hand, the activation of p52 and c-Rel by Tax at the late phase is accompanied by an elevation in their mRNA and protein. This activation is most likely due to the function of Tax to κB-responsive elements in the promoters of p52 and c-Rel. Therefore, it appears that Tax activates NF-κB/Rel both in posttranscriptional and transcriptional steps.

Molecular mechanisms of Tax-mediated NF-κB activation

Three mechanisms have been proposed for Tax-mediated transactivation of the NF-κB binding site: 1) the indirect association of Tax to the NF-κB binding site through interaction with NF-κB p50, RelA, and c-Rel; 2) the interaction of Tax with IκB family members (p105, p100, and IκBs) (Fig. 2); and 3) the activation of IκB kinase (Fig. 3). We will explain the respective mechanisms in more detail in the following sections.

1) Interaction of Tax with NF-κB

Tax binds to p50, RelA, and c-Rel on the NF-κB binding site through the Rel homology domain,[44] and activates transcription.[44,45] These findings indicate that the binding of Tax to Rel subunits in the nucleus potentiates their transactivating potential. However, this mechanism does not explain how Tax induces the nuclear translocation of NF-κB. Tax is principally a nuclear protein, but a fraction of Tax is localized in the cytoplasmic compartment of HTLV-I-infected cells.[46] Nicot et al.[47] showed that Tax mutants which mainly localize in the cytoplasmic compartment can efficiently transactivate the NF-κB pathway, indicating that Tax mainly activates NF-κB through a cytoplasmic event. Thus, the second and third mechanisms, which we will explain below, are believed to be more important.

2) Interaction of Tax with IκBs (Fig. 2)

i) IκBα: The initial effect of Tax on the nuclear translocation of p50/RelA is mediated by the phosphorylation and degradation of IκBα.[43,48] Tax induces the dissociation of the NF-κB/IκBα complex and promoters the nuclear localization of NF-κB subunits.[49] Indeed, a large portion of IκBα is phosphorylated in Tax-expressing or HTLV-I-infected cells, and the steady-state levels of IκBα in these cells are reduced compared with cells not expressing Tax.[48,49] Tax binds to IκBα *in vitro*.[49] The Tax/IκBα complex is detected in Tax-expressing cells.[49] Combined together, these findings suggest the

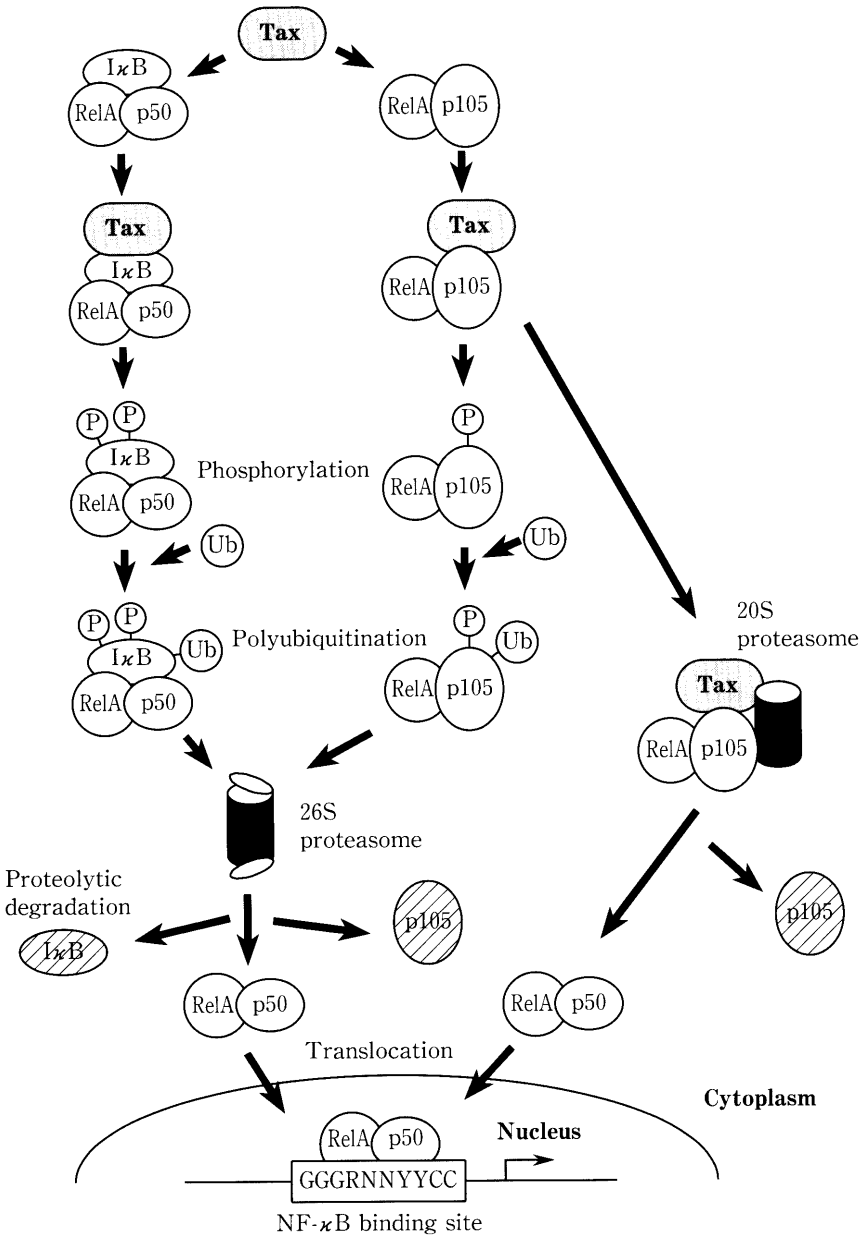

Fig. 2. Molecular mechanisms of NF-κB/Rel activation by Tax. In the cytoplasm, Tax activates signaling pathways that lead to IκBα and IκBβ (IκB) phosphorylation (P). Phosphorylation in turn triggers the polyubiquitousness (Ub) of IκB, which targets IκB for degradation in the 26S proteasome. Tax can associate with IκB molecules such as IκBα, IκBβ, p105, and p100 in the cytoplasm. These interactions may prevent the inhibitory activity of IκB molecules on Rel-containing complexes, which are then freed to translocate into the nucleus and specifically bind to κB binding sites in target genes, and activate transcription. Tax may act as a linker between proteasome subunits (20S proteasome) and p105, thus facilitating the processing of p105 into p50.

physical association of Tax with IκBα.

ii) IκBβ: There are several differences between IκBα and IκBβ.[50] The degradation of IκBα and activation of NF-κB is followed by the enhanced de novo synthesis of the IκBα protein, since NF-κB by itself activates the transcription of IκBα. This auto-

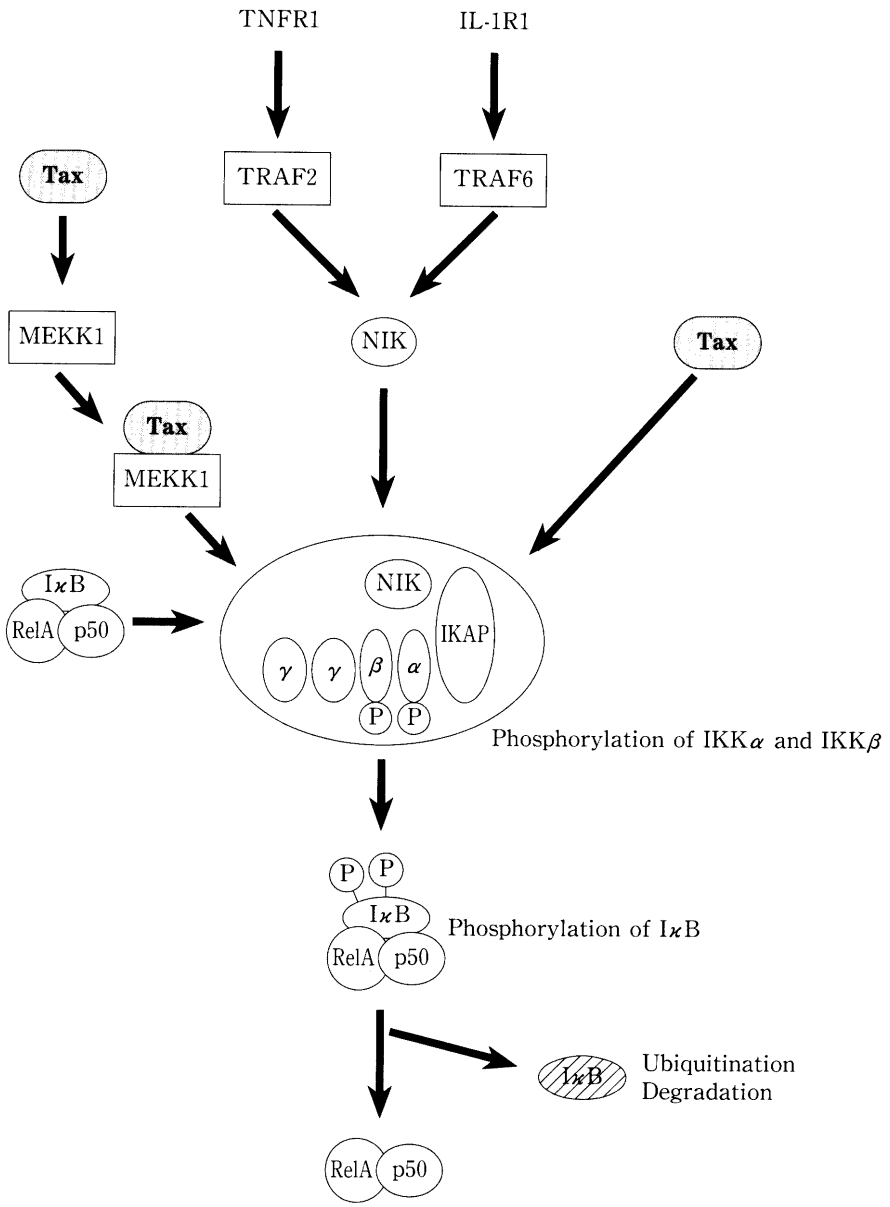

Fig. 3. NIK, IKK, and MEKK1 participate in HTLV-I Tax-mediated NF-κB activation. Tax triggers the activation of cellular protein kinases, IKKα and IKKβ, which phosphorylate IκB, resulting in its degradation and NF-κB activation. TRAF, TNF-receptor-associated factor; NIK, NF-κB-inducing kinase; IKK, IκB kinase; IKAP, IKK-complex-associated protein; MEKK1, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1.

regulatory mechanism ensures that the activation of NF-κB is transient. In contrast to IκBα, the transcription of IκBβ is not under the control of NF-κB. PMA and TNF-α cause a rapid but transient activation of NF-κB by primarily affecting IκBα complexes, whereas LPS and IL-1 cause a persistent activation of NF-κB by affecting both IκBα and IκBβ complexes.[50] Thus, the degradation of IκBβ is associated with the persistent nuclear expression of NF-κB/Rel.[50] The levels of IκBβ are reduced in Tax-expressing or HTLV-I-infected cells,[51,52] perhaps accounting for the appearance of a persistently high level of nuclear expression of NF-κB complexes in Tax-expressing or HTLV-I-infected cell lines.

iii) p105, p100, and IκBγ: All IκB proteins contain multiple regions of homology known as the ankyrin-repeat motifs. p105 and p100 also contain ankyrin-repeats and are included in the IκB family. Tax directly binds to p105 and p100,[53,54] but shows a higher affinity toward p100 than p105.[53,55-57] The N-terminus Rel homology domain of p100 mediates this interaction. Tax has also been reported to stimulate the release of p105 from p50 and RelA, thereby allowing the nuclear translocation of the active NF-κB complex.[58,59] Tax may also facilitate p105 degradation by linking it to the 20 S proteasome subunit.[60] In this regard, Kanno et al.[57] and Munoz et al.[59] reported that Tax can overcome the inhibitory effect of p100 on Rel subunits, but other investigators have failed to detect any substantial effect of Tax on the IκB activity of p100.[53,56,61] The different results obtained in these studies may reflect methodological differences.

IκBγ is the product of an alternate promoter usage that produces and mRNA encoding the C-terminal portion of p105. Tax also interacts with IκBγ through its ankyrin motifs and induces the dissociation of IκBγ from a complex with NF-κB proteins, inducing the nuclear translocation of NF-κB proteins.[62] However, IκBγ protein has never been detected in human T cells.

3) Interaction of Tax with IκB kinase (IKK) complex (Fig. 3)

i) IKKα and IKKβ: Two kinases that phosphorylate IκBs (IKK; IKKα and IKKβ) have been purified and cloned. The deduced amino acid sequence showed that they contain an N-terminal protein kinase domain and a C-terminal regulatory domain with several protein-protein interaction motifs.[63-65] IKKα and IKKβ were also identified through a two hybrid screen as proteins that interact with the NF-κB-activating kinase NIK.[66,67] The IKK complex phosphorylates IκBα and IκBβ at each of the two N-terminal serine residues, which in turn trigger their ubiquitousness and degradation. Tax activates both IKKα and IKKβ.[68-70] Endogenous IKK enzymatic activity is elevated in either Tax transfectants or HTLV-I-infected T-cell lines.[68-70] The activity of IKK is also regulated by upstream kinases. NIK and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEKK) 1 are candidates responsible for the regulation of IKK activities. The dominant negative mutant of NIK inhibits Tax-induced IKK activation.[69,70] Tax also binds to the amino terminus of MEKK1 and stimulates MEKK1 kinase activity.[71] The dominant negative mutant of MEKK1 prevents Tax activation of the NF-κB pathway.[71] Tax-mediated activation of IKK might result from a direct interaction of Tax with MEKK1. In this regard, Yin et al.[71] suggested that IKKβ, not IKKα, is required for the Tax activation of NF-κB, while other groups demonstrated that both IKKα and IKKβ are involved in the Tax activation of NF-κB.[68-70] This discrepancy might be due to the different experimental strategies. The activation of NF-κB by Tax does not appear to involve the TNF-receptor-associated factor TRAF2 and TRAF6 adaptor proteins which represent more proximal components of the TNF-α and IL-1 signaling pathways.[69] These findings suggest that the distal components of the signaling pathway of proinflammatory cytokines are selectively coopted by Tax, leading to the activation of NF-κB.

ii) IKKγ: Recently, Rothwarf et al.[72] purified a third subunit from the IKK complex, termed IKKγ (Fig. 3). IKKγ is not a kinase, and directly interacts preferentially with IKKβ. The core IKK complex might consist of an IKKα-IKKβ heterodimer associated with an IKKγ dimer or trimer. IKKγ is required for activation of the IKK complex. NF-κB essential modifier (NEMO) is the mouse homologue of IKKγ, and was cloned by using a flat revertant cell line 5R of a Tax transformed Rat-1 fibroblastic cell line.[73] The mutation of NEMO in a revertant was accompanied by the disappearance of Tax-induced NF-κB activity and the transformed phenotype in Rat-1. NEMO is essential for the activation of NF-κB not only by Tax but also by LPS, PMA, and IL-1. These data also suggest that the activation of NF-κB by Tax occurs in or upstream of the IKK complex.

2. Tax-independent pathway for the induced nuclear expression of NF-κB p50 and RelA in the ATL leukemic cells *in vivo*

Constitutive activation of NF-κB in primary ATL cells

Leukemic cells of ATL patients express very low levels of viral genes including Tax, suggesting that the expression of viral proteins is not necessary for leukemic proliferation at the late stage of the disease. However, several genes that can be transactivated by Tax are also constitutively expressed in leukemic cells from ATL patients, probably by a Tax-independent mechanism. For instance, ATL cells *in vivo* display surface IL-2Rα[74] and express mRNA for cytokines including IL-1α,[75,76] IL-1β,[75-77] IL-6,[23,78] IL-8,[79] IL-9,[80] IL-10,[81] TNF-β,[82] transforming growth factor β,[83,84] and parathyroid hormone-related protein.[85,86] Among these, genes for IL-2Rα,[19] IL-1α,[87], IL-6,[23] IL-8,[88] and TNF-β,[89] harbor the κB

Table 1. Characteristics of T-cell lines

Cell line	Origin	HTLV-I provirus	Tax	IL-2Rα	IκBα turnover	NF-κB
Jurkat	ALL	−	−	−	→	−
MOLT-4	ALL	−	−	−	→	−
H-9	CTCL	−	−	−	→	−
MT-2	Cord[a]	+	+	+	↑	p50/c-Rel
HUT-102	?	+	+	+	↑	p50/c-Rel
SLB-1	Normal[a]	+	+	+	↑	p50/c-Rel
TL-OmI	ATL	+	−	+	↑	p50/RelA
C5/MJ	Cord[a]	+	+	+	↑	p50/c-Rel

ALL, acute lymphoblastic leukemia; CTCL, cutaneous T-cell lymphoma.
[a]Established by cocultivation of cord blood or normal peripheral blood lymphocytes with HTLV-I-infected cells.

enhancer element, and Tax activates the transcription of these celular genes through the NF-κB binding site. Recently, we found that leukemic cells from ATL patients *in vivo*, such as HTLV-I-infected T-cell lines *in vitro*, display a constitutive NF-κB DNA binding activity and increased degradation of IκBα.[90] Thus, the NF-κB/IκBα pathway is activated in leukemic cells of ATL patients *in vivo*, which may account for the persistent expression of certain cellular genes.

Tax-independent pathway for induction of the nuclear expression of NF-κB p50 and RelA proteins in ATL cells

TL-OmI is established from peripheral blood mononuclear cells of ATL patients. We first confirmed that this cell line originates from leukemic cells of these patients. We next examined the composition of NF-κB in this cell line as well as four other HTLV-I-transformed cell lines (Table 1) . Four HTLV-I-transformed cell lines (MT-2, HUT-102, SLB-1, and C5/MJ) expressed detectable viral mRNA and Tax protein. The NF-κB binding activity in these four cell lines consisted mostly of p50/c-Rel. TL-OmI also displayed a constitutive NF-κB activity, despite the lack of any detectable Tax expression. Interestingly, NF-κB in TL-OmI consists of p50/p50 and p50/p65 like that in fresh primary leukemic cells. These results suggest that the activation of NF-κB occurs through a Tax-independent mechanism in leukemic cells of ATL patients and in TL-OmI, possibly due to a differential NF-κB subunit activation.

3. Role of NF-κB activation in T cell transformation by HTLV-I

It is still unclear at present whether Tax-induced NF-κB activation is involved in cell transformation. Contradictory findings have been reported concerning the importance of NF-κB activation for transformation of the rodent fibroblast by Tax. Smith and Greene[14] suggested that the CREB/ATF pathway but not the NF-κB one plays an important role in such transformation, while others[91-93] suggested that the activation of NF-κB is essential for the transformation. The conflicting results on cell transformation might be attributed to certain differences in the cells used for the transformation assay. In this regard, we have suggested that either the NF-κB or CArG box (SRF) pathways may operate in cell transformation, depending on the cell type used for the assay.[93] In a recent study using transgenic mice carrying the *tax* gene, Coscoy et al.[94] showed that the constitutive expression of Tax leads to a continuous activation of NF-κB in fibrosarcoma-derived murine cells. This NF-κB activation was essential for cell transformation, as shown by expressing a nondegradable mutant of IκBβ in these cells. Furthermore, NEMO (IKKγ) is the responsible gene for the flat-revertant (5R) of a Tax transformed fibroblastic cell line.[73] The 5R cells regain a transformed phenotype when stably transfected with NEMO. These reports strongly indicate an essential role for the nuclear expression of active NF-κB in cell transformation by Tax.

Using retroviral vectors, Akagi et al.[95] demonstrated a critical role for NF-κB activation in the IL-2 dependent transformation of human primary $CD4^+$ T cells by Tax. Interestingly, a Tax mutant

which is active for the NF-κB pathway but not for CREB/ATF one preferentially transformed $CD8^+$ cells but not $CD4^+$ cells, indicating the indispensable role of a CREB/ATF pathway in the preferential growth of $CD4^+$ cells. Thus, the clonal expansion of $CD4^+$ T cells by Tax requires the combination of these two pathways. Recently, we showed that Tax converts the cell growth of a mouse T-cell line from being IL-2 dependent to IL-2 independent, and that the NF-κB pathway but not CREB/ATF one is essential for IL-2 independent growth.[107] Thus, Tax plays a crucial role in IL-2 independent T cell transformation induced by HTLV-I as well as in IL-2 dependent growth.

4. NF-κB/Rel and apoptosis

ATL shows a poor response to chemotherapy, and the survival rate of ATL patients is low compared with other leukemias.[96] The emergence of drug-resistant leukemic cells may explain the poor response. HTLV-I-transformed T-cell lines are significantly more resistant to apoptotic stimuli including anti-Fas antibody, ultraviolet irradiation, and chemotherapeutic agents, than uninfected T-cells,[28,97,98] Constitutive NF-κB activity is essential for cell survival in a number of different cell types[99] and the inhibition of NF-κB using protease inhibitors or the expression of a trans-dominant mutant form of IκBα which is more resistant to proteasome degradation facilitates apoptosis in various cell types.[100–102] Thus, the constitutive NF-κB activity in ATL cells may be responsible for the poor response to chemotherapy.

The constitutive activation of NF-κB/Rel is found in leukemic cells of most B cell chronic lymphocytic leukemia (B-CLL) patients like ATL.[103–105] Aspirin and salicylate induce apoptosis in B-CLL cells.[106] Proteasome inhibitors also induce apoptosis in B-CLL.[103,104] Because these reagents can block the induction of NF-κB proteins, the inhibition of NF-κB activity by these reagents might induce apoptosis in B-CLL cells. Indeed, proteasome inhibitors drastically reduce the levels of active NF-κB in B-CLL cells.[103] These examples support the potential use of NF-κB/Rel inhibitors as antitumor agents. We are currently investigating whether nonsteroidal anti-inflammatory drugs and proteasome inhibitors are useful in the treatment of ATL.

Conclusion

HTLV-I activates transcription factor NF-κB through mechanisms that involve the cytoplasmic inactivation of inhibitory IκB molecules. The NF-κB pathway regulates the activation of many cytokines and some of their receptors, growth factors, cell adhesion molecules, and proto-oncogenes, which are expected to be involved in the immortalization or transformation of T cells by HTLV-I. NF-κB has also recently been shown to play an active role in counteracting apoptotic signals and promoting cell survival. Tax may cause early T cell proliferation by the activation of NF-κB, although the responsible genes linked to such a process remain unidentified. *In vivo*, most ATL cells do not express significant levels of Tax. We believe that Tax-independent mechanisms operate for constitutive NF-κB activation in leukemic cells of ATL patients *in vivo*. During later stages of leukemogenesis, activation of NF-κB, but not Tax, may be required for the maintenance of leukemic phenotypes of ATL cells.

Acknowledgments. This work is supported by a Grant-in-Aid for the Encouragement of Young Scientists from the Ministry of Education, Science, Sports and Culture of Japan, and a Cooperative Research Grant No. 1998-10-A-14 from the Institute of Tropical Medicine, Nagasaki University.

References

1) Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita K, Shirakawa S, Miyoshi I: Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci USA* **78:** 6476-6480, 1981.
2) Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA* **77:** 7415-7419, 1980.
3) Yoshida M, Seiki M, Yamaguchi K, Takatsuki K: Monoclonal integration of human T-cell leukemia provirus in all primary tumors of adult T-cell leukemia suggests causative role of human T-cell leukemia virus in the disease. *Proc Natl Acad Sci USA* **81:** 2534-2537, 1984.
4) Gassain A, Barin F, Vernant JC, Gout O, Marus L, Calender A, de The G: Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet* **2:** 407-410, 1985.
5) Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M: HTLV-I associated myelopathy, a new clinical entity. *Lancet* **1:** 1031-1032, 1986.
6) Mochizuki M, Watanabe T, Yamaguchi K, Takatsuki K, Yoshimura K, Shirao M, Nakashima S, Mori

S, Araki S, Miyata N: HTLV-I uveitis: a distinct clinical entity caused by HTLV-I. *Jpn J Cancer Res* **83:** 236-239, 1992.
7) Nishioka K, Maruyama I, Sato K, Kitajima I, Nakajima Y, Osame M: Chronic inflammatory arthropathy associated with HTLV-I. *Lancet* **1:** 441, 1989.
8) Terada K, Katamine S, Eguchi K, Moriuchi R, Kita M, Shimada H, Yamashita I, Iwata K, Tsuji Y, Nagataki S, Miyamoto T: Prevalence of serum and salivary antibodies to HTLV-1 in Sjögren's syndrome. *Lancet* **344:** 1116-1119, 1994.
9) LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W: Infective dermatitis of Jamaican children: a marker for HTLV-I infection. *Lancet* **336:** 1345-1347, 1990.
10) Leon-Monzon M, Illa I, Dalakas MC: Polymyositis in patients infected with human T-cell leukemia virus type I: the role of the virus in the cause of the disease. *Ann Neurol* **36:** 643-649, 1994.
11) Seiki M, Hattori S, Hirayama Y, Yoshida M: Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA. *Proc Natl Acad Sci USA* **80:** 3618-3622, 1983.
12) Seiki M, Eddy R, Shows TB, Yoshida M: Nonspecific integration of the HTLV provirus genome into adult T-cell leukaemia cells. *Nature* **309:** 640-642, 1984.
13) Grassmann R, Berchtold S, Radant I, Alt M, Fleckenstein B, Sodroski JG, Haseltine WA, Ramstedt U: Role of human T-cell leukemia virus type 1 X region proteins in immortalization of primary human lymphocytes in culture. *J Virol* **66:** 4570-4575, 1992.
14) Smith MR, Greene WC: Type I human T cell leukemia virus tax protein transforms rat fibroblasts through the cyclic adenosine monophosphate response element binding protein/activating transcription factor pathway. *J Clin Invest* **88:** 1038-1042, 1991.
15) Tanaka A, Takahashi C, Yamaoka S, Nosaka T, Maki M, Hatanaka M: Oncogenic transformation by the *tax* gene of human T-cell leukemia virus type I *in vitro*. *Proc Natl Acad Sci USA* **87:** 1071-1075, 1990.
16) Hinrichs SH, Nerenberg M, Reynolds RK, Khoury G, Jay G: A transgenic mouse model for human neurofibromatosis. *Science* **237:** 1340-1343, 1987.
17) Nerenberg M, Hinrichs SH, Reynolds RK, Khoury G, Jay G: The tat gene of human T-lymphotropic virus type 1 induces mesenchymal tumors in transgenic mice. *Science* **237:** 1324-1329, 1987.
18) Grossman WJ, Kimata JT, Wong F-H, Zutter M, Ley TJ, Ratner L: Development of leukemia in mice transgenic for the *tax* gene of human T-cell leukemia virus type I. *Proc Natl Acad Sci USA* **92:** 1057-1061, 1995.
19) Ballard DW, Bohnlein E, Lowenthal JW, Wano Y, Franza BR, Greene WC: HTLV-I tax induces cellular proteins that activate the κB element in the IL-2 receptor α gene. *Science* **241:** 1652-1655, 1988.
20) Fujii M, Niki T, Mori T, Matsuda T, Matsui M, Nomura N, Seiki M: HTLV-1 Tax induces expression of various immediate early serum responsive genes. *Oncogene* **6:** 1023-1029, 1991.
21) Fujii M, Sasson-Corsi P, Verma IM: c-*fos* promoter trans-activation by the tax1 protein of human T-cell leukemia virus type I. *Proc Natl Acad Sci USA* **85:** 8526-8530, 1988.
22) Siekevitz M, Feinberg MB, Holbrook N, Wong-Staal F, Greene WC: Activation of interleukin 2 and interleukin 2 receptor (Tac) promoter expression by the trans-activator (*tat*) gene product of human T-cell leukemia virus type I. *Proc Natl Acad Sci USA* **84:** 5389-5393, 1987.
23) Mori N, Shirakawa F, Shimizu H, Murakami S, Oda S, Yamamoto K, Eto S: Transcriptional regulation of the human interleukin-6 gene promoter in human T-cell leukemia virus type I-infected T cell lines: evidence for the involvement of NF-κB. *Blood* **84:** 2904-2911, 1994.
24) Duyao MP, Kessler DJ, Spicer DB, Bartholomew C, Cleveland JL, Siekevitz M, Sonenshein GE: Transactivation of the c-*myc* promoter by human T cell leukemia virus type 1 *tax* is mediated by NFκB. *J Biol Chem* **267:** 16288-16291, 1992.
25) Miyatake S, Seiki M, Yoshida M, Arai K: T-cell activation signals and human T-cell leukemia virus type I-encoded $p40^x$ protein activate the mouse granulocyte-macrophage colony-stimulating factor gene through a common DNA element. *Mol Cell Biol* **8:** 5581-5587, 1988.
26) Mori N, Murakami S, Oda S, Eto S: Human T-cell leukemia virus type I Tax induces intracellular adhesion molecule-1 expression in T cells. *Blood* **84:** 350-351, 1994.
27) Valentin H, Lemasson I, Hamaia S, Casse H, Konig S, Devaux C, Gazzolo L: Transcriptional activation of the vascular cell adhesion molecule-1 gene in T lymphocytes expressing human T-cell leukemia virus type 1 Tax protein. *J Virol* **71:** 8522-8530, 1997.
28) Brauweiler A, Garrus JE, Reed JC, Nyborg JK: Repression of Bax gene expression by the HTLV-I Tax protein: implications for suppression of apoptosis in virally infected cells. *Virology* **231:** 135-140. 1997.
29) Jeang K-T, Widen SG, Semmes OJ IV, Wilson SH: HTLV-I trans-activator protein, Tax, is a trans-repressor of the human β-polymerase gene. *Science* **247:** 1082-1084, 1990.
30) Uittenbogaard MN, Giebler HA, Reisman D, Nyborg JK: Transcriptional repression of *p53* by human T-cell leukemia virus type I Tax protein. *J Biol Chem* **270:** 28503-28506, 1995.
31) Feigenbabaum L, Fujita K, Collins FS, Jay G: Repression of the *NF1* gene by Tax may explain the development of neurofibromas in human T-

lymphotropic virus type 1 transgenic mice. *J Virol* **70:** 3280-3285, 1996.
32) Uittenbogaard MN, Armstrong AP, Chiaramello A, Nyborg JK: Human T-cell leukemia virus type I Tax protein represses gene expression through the basic helix-loop-helix family of transcription factors. *J Biol Chem* **269**: 22466-22469, 1994.
33) Caron C, Rousset R, Beraud C, Moncollin V, Egly J-M, Jalinot P: Functional and biochemical interaction of the HTLV-I Taxl transactivator with TBP. *EMBO J* **12:** 4269-4278, 1993.
34) Kwok RP, Laurance ME, Lundblad JR, Goldman PS, Shih H, Connor LM, Marriott SJ, Goodman RH: Control of cAMP-regulated enhancers by the viral transactivator Tax through CREB and the co-activator CBP. *Nature* **380:** 642-646, 1996.
35) Anderson MG, Dynan WS: Quantitative studies of the effect of HTLV-I Tax protein on CREB protein-DNA binding. *Nucleic Acids Res* **22:** 3194-3201, 1994.
36) Baranger AM, Palmer CR, Hamm MK, Giebler HA, Brauweiler A, Nyborg JK, Schepartz A: Mechanism of DNA-binding enhancement by the human T-cell leukaemia virus transactivator Tax. *Nature* **376:** 606-608, 1995.
37) Wagner S, Green MR: HTLV-I Tax protein stimulation of DNA binding of bZIP proteins by enhancing dimerization. *Science* **262:** 395-399, 1993.
38) Suzuki T, Kitao S, Matsushime H, Yoshida M: HTLV-1 Tax protein interacts with cyclin-dependent kinase inhibitor $p16^{INK4A}$ and counteracts its inhibitory activity towards CDK4. *EMBO J* **15:** 1607-1614, 1996.
39) Baeuerle PA, Baltimore D: NF-κB: ten years after. *Cell* **87:** 13-20, 1996.
40) Ghosh S, May MJ, Kopp EB: NF-κB and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu Rev Immunol* **16:** 225-260, 1998.
41) Verma IM, Stevenson JK, Schwarz EM, Van Antwerp D, Miyamoto S: Rel/NF-κB/IκB family: intimate tales of association and dissociation. *Genes Dev* **9:** 2723-2735, 1995.
42) Palombella VJ, Rando OJ, Goldberg AL, Maniatis T: The ubiquitin-proteasome pathway is required for processing the NF-κB1 precursor protein and the activation of NF-κB. *Cell* **78:** 773-785, 1994.
43) Kanno T, Brown K, Franzoso G, Siebenlist U: Kinetic analysis of human T-cell leukemia virus type I Tax-mediated activation of NF-κB. *Mol Cell Biol* **14:** 6443-6451, 1994.
44) Suzuki T, Hirai H, Yoshida M: Tax protein of HTLV-1 interacts with the Rel homology domain of NF-κB p65 and c-Rel proteins bound to the NF-κB binding site and activates transcription. *Oncogene* **9:** 3099-3105, 1994.
45) Suzuki T, Hirai H, Fujisawa J, Fujita T, Yoshida M: A trans-activator Tax of human T-cell leukemia virus type 1 binds to NF-κB p50 and serum response factor (SRF) and associates with enhancer DNAs of the NF-κB site and CArG box. *Oncogene* **8:** 2391-2397, 1993.
46) Goh WC, Sodroski J, Rosen C, Essex M, Haseltine WA: Subcellular localization of the product of the long open reading frame of human T-cell leukemia virus type I. *Science* **227:** 1227-1228, 1985.
47) Nicot C, Tie F, Giam C-Z: Cytoplasmic forms of human T-cell leukemia virus type 1 Tax induce NF-κB activation. *J Virol* **72:** 6777-6784, 1998.
48) Sun S-C, Elwood J, Beraud C, Greene WC: Human T-cell leukemia virus type I Tax activation of NF-κB/Rel involves phosphorylation and degradation of IκBα and RelA (p65) -mediated induction of the c-*rel* gene. *Mol Cell Biol* **14:** 7377-7384, 1994.
49) Suzuki T, Hirai H, Murakami T, Yoshida M: Tax protein of HTLV-1 destabilizes the complexes of NF-κB and IκB-α and induces nuclear translocation of NF-κB for transcriptional activation. *Oncogene* **10:** 1199-1207, 1995.
50) Thompson JE, Phillips RJ, Erdjument-Bromage H, Tempst P, Ghosh S: IκB-β regulates the persistent response in a biphasic activation of NF-κB. *Cell* **80:** 573-582, 1995.
51) Good L, Sun S-C: Persistent activation of NF-κB/Rel by human T-cell leukemia virus type 1 Tax involves degradation of IκBβ. *J Virol* **70:** 2730-2735, 1996.
52) McKinsey TA, Brockman JA, Scherer DC, Al-Murrani SW, Green PL, Ballard DW: Inactivation of IκBβ by the Tax protein of human T-cell leukemia virus type 1: a potential mechanism for constitutive induction of NF-κB. *Mol Cell Biol* **16:** 2083-2090, 1996.
53) Murakami T, Hirai H, Suzuki T, Fujisawa J, Yoshida M: HTLV-I Tax enhances NF-κB2 expression and binds to the products p52 and p100, but does not suppress the inhibitory function of p100. *Virology* **206:** 1066-1074, 1995.
54) Hirai H, Fujisawa J, Suzuki T, Ueda K, Muramatsu M, Tsuboi A, Arai N, Yoshida M: Transcriptional activator Tax of HTLV-1 binds to the NF-κB precursor p105. *Oncogene* **7:** 1737-1742, 1992.
55) Lanoix J, Lacoste J, Pepin N, Rice N, Hiscott J: Overproduction of NFKB2 (*lyt-10*) and c-Rel: a mechanism for HTLV-I Tax-mediated *trans*-activation via the NF-κB signalling pathway. *Oncogene* **9:** 841-852, 1994.
56) Beraud C, Sun S-C, Ganchi P, Ballard DW, Greene WC: Human T-cell leukemia virus type I Tax associates with and is negatively regulated by the NF-κB2 p100 gene product: implications for viral latency. *Mol Cell Biol* **14:** 1374-1382, 1994.
57) Kanno T, Franzoso G, Siebenlist U: Human T-cell leukemia virus type I Tax-protein-mediated activation of NF-κB from p100 (NF-κB2) -inhibited cytoplasmic reservoirs. *Proc Natl Acad Sci USA* **91:** 12634-12638, 1994.
58) Watanabe M, Muramatsu M, Hirai H, Suzuki T, Fujisawa J, Yoshida M, Arai K, Arai N: HTLV-I encoded Tax in association with NF-κB precursor

p105 enhances nuclear localization of NF-κB p50 and p65 in transfected cells. *Oncogene* **8:** 2949-2958, 1993.

59) Munoz E, Courtois G, Veschambre P, Jalinot P, Israel A: Tax induces nuclear translocation of NF-κB through dissociation of cytoplasmic complexes containing p105 or p100 but does not induce degradation of IκBα/MAD3. *J Virol* **68:** 8035-8044, 1994.

60) Rousset R, Desbois C, Bantignies F, Jalinot P: Effects on NF-κB1/p105 processing of the interaction between the HTLV-1 transactivator Tax and the proteasome. *Nature* **381:** 328-331, 1996.

61) Watanabe M, Muramatsu M, Tsuboi A, Arai K: Differential response of NF-κB1 p105 and NF-κB2 p100 to HTLV-I encoded Tax. *FASEB Lett* **342:** 115-118, 1994.

62) Hirai H, Suzuki T, Fujisawa J, Inoue J, Yoshida M: Tax protein of human T-cell leukemia virus type I binds to the ankyrin motifs of inhibitory factor κB and induces nuclear translocation of transcription factor NF-κB proteins for transcriptional activation. *Proc Natl Acad Sci USA* **91:** 3584-3588, 1994.

63) DiDonato JA, Hayakawa M, Rothwarf DM, Zandi E, Karin M: A cytokine-reponsive IκB kinase that activates the transcription factor NF-κB. *Nature* **388:** 548-554, 1997.

64) Zandi E, Rothwarf DM, Delhase M, Hayakawa M, Karin M: The IκB kinase complex (IKK) contains two kinase subunits, IKKα and IKKβ, necessary for IκB phosphorylation and NF-κB activation. *Cell* **91:** 243-252, 1997.

65) Mercurio F, Zhu H, Murray BW, Shevchenko A, Bennett BL, Li J, Young DB, Barbosa M, Mann M, Manning A, Rao A: IKK-1 and IKK-2: cytokine-activated IκB kinases essential for NF-κB activation. *Science* **278:** 860-866, 1997.

66) Regnier CH, Song HY, Gao X, Goeddel DV, Cao Z, Rothe M: Identification and characterization of an IκB kinase. *Cell* **90:** 373-383, 1997.

67) Woronicz JD, Gao X, Cao Z, Rothe M, Goeddel DV: IκB kinase-β: NF-κB activation and complex formation with IκB kinase-α and NIK. *Science* **278:** 866-869, 1997.

68) Chu Z-L, DiDonato JA, Hawiger J, Ballard DW: The Tax oncoprotein of human T-cell leukemia virus type 1 associates with and persistently activates IκB kinases containing IKKα and IKKβ. *J Biol Chem* **273:** 15891-15894, 1998.

69) Geleziunas R, Ferrell S, Lin X, Mu Y, Cunningham ET Jr, Grant M, Connelly MA, Hambor JE, Marcu KB, Greene WC: Human T-cell leukemia virus type 1 Tax induction of NF-κB involves activation of the IκB kinasa α (IKKα) and IKKβ cellular kinases. *Mol Cell Biol* **18:** 5157-5165, 1998.

70) Uhlik M, Good L, Xiao G, Harhaj EW, Zandi E, Karin M, Sun S-C: NF-κB-inducing kinase and IκB kinase participate in human T-cell leukemia virus I Tax-mediated NF-κB activation. *J Biol Chem* **273:** 21132-21136, 1998.

71) Yin M-J, Christerson LB, Yamamoto Y, Kwak Y-T, Xu S, Mercurio F, Barbosa M, Cobb MH, Gaynor RB: HTLV-I Tax protein binds to MEKK1 to stimulate IκB kinase activity and NF-κB activation. *Cell* **93:** 875-884, 1998.

72) Rothwarf DM, Zandi E, Natoli G, Karin M: IKK-γ is an essential regulatory subunit of the IκB kinase complex. *Nature* **395:** 297-300, 1998.

73) Yamaoka S, Courtois G, Bessia C, Whiteside ST, Weil R, Agou F, Kirk HE, Kay RJ, Israel A: Complementation cloning of NEMO, a component of the IκB kinase complex essential for NF-κB activation. *Cell* **93:** 1231-1240, 1998.

74) Uchiyama T, Hori T, Tsudo M, Wano Y, Umadome H, Tamori S, Yodoi J, Maeda M, Sawami H, Uchino H: Interleukin-2 receptor (Tac antigen) expressed on adult T cell leukemia cells. *J Clin Invest* **76:** 446-453, 1985.

75) Kodaka T, Uchiyama T, Umadome H, Uchino H: Expression of cytokine mRNA in leukemic cells from adult T cell leukemia patients. *Jpn J Cancer Res* **80:** 531-536, 1989.

76) Mori N, Shirakawa F, Murakami S, Oda S, Eto S: Interleukin-4 inhibits the production of interleukin-1 by adult T-cell leukemia cells. *Eur J Haematol* **55:** 121-125, 1995.

77) Wano Y, Hattori T, Matsuoka M, Takatsuki K, Chua AO, Gubler U, Greene WC: Interleukin 1 gene expression in adult T cell leukemia. *J Clin Invest* **80:** 911-916, 1987.

78) Mori N, Shirakawa F, Murakami S, Oda S, Eto S: Inhibitory effect of interleukin 4 on production of interleukin 6 by adult T-cell leukemia cells. *Cancer Res* **53:** 4643-4647, 1993.

79) Mori N, Murakami S, Oda S, Prager D, Eto S: Production of interleukin 8 in adult T-cell leukemia cells: possible transactivation of the interleukin 8 gene by human T-cell leukemia virus type I *tax*. *Cancer Res* **55:** 3592-3597, 1995.

80) Matsushita K, Arima N, Ohtsubo H, Fujiwara H, Hidaka S, Fukumori J, Tanaka H: Frequent expression of interleukin-9 mRNA and infrequent involvement of interleukin-9 in proliferation of primary adult T-cell leukemia cells and HTLV-I infected T-cell lines. *Leukemia Res* **21:** 211-216, 1997.

81) Mori N, Gill PS, Mougdil T, Murakami S, Eto S, Prager D: Interleukin-10 gene expression in adult T-cell leukemia. *Blood* **88:** 1035-1045, 1996.

82) Ishibashi K, Ishitsuka K, Chuman Y, Otsuka M, Kuwazuru Y, Iwahashi M, Utsunomiya A, Hanada S, Sakurami T, Arima T: Tumor necrosis factor-β in the serum of adult T-cell leukemia with hypercalcemia. *Blood* **77**: 2451-2455, 1991.

83) Niitsu Y, Urushizaki Y, Koshida Y, Terui K, Mahara K, Kohgo Y, Urushizaki I: Expression of TGF-beta in adult T cell leukemia. *Blood* **71:** 263-266, 1988.

84) Kim S-J, Kehrl JH, Burton J, Tendler CL, Jeang

K-T, Danielpour D, Thevenin C, Kim KY, Sporn MB, Roberts AB: Transactivation of the transforming growth factor β1 (TGF-β1) gene by human T lymphotropic virus type 1 Tax: a potential mechanism for the increased production of TGF-β1 in adult T cell leukemia. *J Exp Med* **172:** 121-129, 1990.

85) Watanabe T, Yamaguchi K, Takatsuki K, Osame M, Yoshida M: Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type 1 (HTLV-I) carriers and adult T cell leukemia patients that can be *trans*-activated by HTLV-1 *tax* gene. *J Exp Med* **172:** 759-765, 1990.

86) Mori N, Ohsumi K, Murakami S, Wake A, Shirakawa F, Morimoto I, Oda S, Eto S: Enhancing effect of interleukin-2 on production of parathyroid hormone-related protein by adult T-cell leukemia cells. *Jpn J Cancer Res* **84:** 425-430, 1993.

87) Mori N, Prager D: Transactivation of the interleukin-1α promoter by human T-cell leukemia virus type I and type II Tax proteins. *Blood* **87:** 3410-3417, 1996.

88) Mori N, Mukaida N, Ballard DW, Matsushima K, Yamamoto N: Human T-cell leukemia virus type I Tax transactivates human *interleukin* 8 gene through acting concurrently on AP-1 and nuclear factor-κB-like sites. *Cancer Res* **58:** 3993-4000, 1998.

89) Tschachler E, Bohnlein E, Felzman S, Reitz MJ: Human T lymphotropic virus type I tax regulates the expression of the human lymphotoxin gene. *Blood* **81:** 95-100, 1993.

90) Mori N, Fujii M, Ikeda S, Yamada Y, Tomonaga M, Ballard DW, Yamamoto N: Constitutive activation of NF-κB in primary adult T-cell leukemia cells. *Blood* **93:** 2360-2368, 1999.

91) Kitajima I, Shinohara T, Bilakovics J, Brown DA, Xu X, Nerenberg M: Ablation of transplanted HTLV-1 Tax-transformed tumors in mice by antisense inhibition of NF-κB. *Science* **258:** 1792-1795, 1992.

92) Yamaoka S, Inoue H, Sakurai M, Sugiyama T, Hazama M, Yamada T, Hatanaka M: Constitutive activation of NF-κB is essential for transformation of rat fibroblasts by the human T-cell leukemia virus type I Tax protein. *EMBO J* **15:** 873-887, 1996.

93) Matsumoto K, Shibata H, Fujisawa J, Inoue H, Hakura A, Tsukahara T, Fujii M: Human T-cell leukemia virus type 1 Tax protein transforms rat fibroblasts via two distinct pathways. *J Virol* **71:** 4445-4451, 1997.

94) Coscoy L, Gonzalez-Dunia D, Tangy F, Syan S, Brahic M, Ozden S: Molecular mechanism of tumorigenesis in mice transgenic for the human T cell leukemia virus *Tax* gene. *Virology* **248:** 332-341, 1998.

95) Akagi T, Ono H, Nyunoya H, Shimotohno K: Characterization of peripheral blood T-lymphocytes transduced with HTLV-I Tax mutants with different trans-activating phenotypes. *Oncogene* **14:** 2071-2078, 1997.

96) Shimoyama M: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma: a report from the Lymphoma Study Group (1984-1987). *Br J Haematol* **79:** 428-437, 1991.

97) Copeland KFT, Haaksma AGM, Goudsmit J, Krammer PH, Heeney JL: Inhibition of apoptosis in T cells expressing human T cell leukemia virus type I Tax. *AIDS Res Hum Retroviruses* **10:** 1259-1268, 1994.

98) Arai M, Kannagi M, Matsuoka M, Sato T, Yamamoto N, Fujii M: Expression of FAP-1 (Fas-associated phosphatase) and resistance to Fas-mediated apoptosis in T cell lines derived from human T cell leukemia virus type 1-associated myelopathy/tropical spastic paraparesis patients. *AIDS Res Hum Retroviruses* **14:** 261-267, 1998

99) Wu M, Lee H, Bellas RE, Schauer SL, Arsura M, Katz D, FitzGerald MJ, Rothstein TL, Sherr DH, Sonenshein GE: Inhibition of NF-κB/Rel induces apoptosis of murine B cells. *EMBO J* **15:** 4682-4690, 1996.

100) Beg AA, Baltimore D: An essential role for NF-κB in preventing TNF-α-induced cell death. *Science* **274:** 782-784, 1996.

101) Wang C-Y, Mayo MW, Baldwin AS Jr: TNF- and cancer therapy-induced apoptosis: potentiation by inhibition of NF-κB. *Science* **274:** 784-787, 1996.

102) Van Antwerp DJ, Martin SJ, Kafri T, Green DR, Verma IM: Suppression of TNF-α-induced apoptosis by NF-κB. *Science* **274:** 787-789, 1996.

103) Chandra J, Niemer I, Gilbreath J, Kliche K-O, Andreeff M, Freireich EJ, Keating M, McConkey DJ: Proteasome inhibitors induce apoptosis in glucocorticoid-resistant chronic lymphocytic leukemic lymphocytes. *Blood* **92:** 4220-4229, 1998.

104) Delic J, Masdehors P, Omura S, Cosset J-M, Dumont J, Binet J-L, Magdelenat H: The proteasome inhibitor lactacystin induces apoptosis and sensitizes chemo- and radioresistant human chronic lymphocytic leukaemia lymphocytes to TNF-α-initiated apoptosis. *Br J Cancer* **77:** 1103-1107, 1998.

105) Romano MF, Lamberti A, Tassone P, Alfinito F, Costantini S, Chiurazzi F, Defrance T, Bonelli P, Tuccillo F, Turco MC, Venuta S: Triggering of CD40 antigen inhibits fludarabine-induced apoptosis in B chronic lymphocytic leukemia cells. *Blood* **92:** 990-995, 1998.

106) Bellosillo B, Pique M, Barragan M, Castano E, Villamor N, Colomer D, Montserrat E, Pons G, Gil J: Aspirin and salicylate induce apoptosis and activation of caspases in B-cell chronic lymphocytic leukemia cells. *Blood* **92:** 1406-1414, 1998.

107) Iwanaga Y, Tsukahara T, Ohashi T, Tanaka Y, Arai M, Nakamura M, Ohtani K, Koya Y, Kannagi M, Yamamoto N, Fujii M: Human T-cell leukemia virus type 1 Tax protein abrogates interleukin-2 dependence in a mouse T-cell line. *J Virol* **73:** 1271-1277, 1999.