Constitutive Activation of TAK1 by HTLV-1 Tax-dependent Overexpression of TAB2 Induces Activation of JNK-ATF2 but Not IKK-NF-κB

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HTLV-1 Tax oncoprotein induces persistent activation of the transcription factor NF-κB and CREB (cAMP-response element-binding protein)/ATF. Transforming growth factor-β-activated kinase 1 (TAK1) has been shown to play a critical role in these transcription factors. Here, we found that TAK1 was constitutively activated in Tax-positive HTLV-1-transformed T cells. Tax induced persistent overexpression of TAK1-binding protein 2 (TAB2), but not TAB3, which is essential for TAB2 activation. Surprisingly, TAK1 was not involved in the activation of NF-κB. On the other hand, JNK and p38 mitogen-activated protein kinases were activated by TAK1. In addition, ATF2, but not CREB, was a target for the TAK1-JNK pathway, and p38 negatively regulated TAK1 activity through TAB1 phosphorylation. These results indicate that Tax-mediated TAK1 activation is important for the activation of ATF2 rather than NF-κB.

EXPERIMENTAL PROCEDURES

Antibodies and Reagents—Antibodies against TAK1 (M-579), TAB1 (C-20), TAB2 (K-20), p65 (C-20-G), IKKα (H-744), IKKγ (FL-419), IkBα (C-21), HA tag (Y-11-G), and proliferating cell nuclear antigen (PCNA; PC-10) were obtained from Santa Cruz Biotechnology. Antibodies against phospho-JNK (Thr-183/Tyr-185), phospho-p38 (Thr-180/Tyr-182), phospho-p65 (Ser-536) (93H1), phospho-IκBα (Ser-32/Ser-36), phospho-ATF2 (Thr-69/Thr-71), phospho CREB (Ser-133), ATF2 (20F1), and CREB were purchased from Cell Signaling Technology. Phospho-specific anti-TAK1 (Thr-187) and anti-TAB1 (Ser-438) antibodies are described previously (12, 18). Antibody against TAB3 was generated by immunizing rabbits with the synthetic peptide corresponding to amino acids 635–648 of human TAB3. Antibody against Tax was dissolved in Me2SO, and the final concentration of Me2SO was less than 0.5%.

Human T-cell lymphotropic virus type 1 (HTLV-1)² is known as the cause of adult T-cell leukemia/lymphoma (ATLL). Infection with this virus results in the activation of several transcriptional factors including NF-κB and CREB in host CD4+ T cells. In particular, the activation of NF-κB correlates with the expression of HTLV-1-derived oncoprotein Tax (1). It has been reported that Tax associates with IKKγ to activate IκB kinase (IKK) complex (2).

Transforming growth factor-β-activated kinase 1 (TAK1) is one of the most characterized MAPK kinase kinase family members and is activated by various cellular stresses, including tumor necrosis factor-α (TNF-α) and interleukin-1 (3–13). It has recently been shown that TAK1 participates in diverse cellular functions, including activation and differentiation of T lymphocytes (14–17). TAK1 functions as an upstream stimulatory molecule of the JNK, p38, and IKK signaling pathways. We have reported that phosphorylation at Thr-187 is essential for TAK1 activation, and TAK1-binding protein 1 (TAB1) and TAB2 are important for inducing phosphorylation (18). Cheung et al. (12) report that the association of TAB1 with p38α negatively regulates TAK1 kinase activity by phosphorylating TAB1 at Ser-438, Thr-431, and Ser-438. On the other hand, TAB2 functions as an adaptor protein to recruit TAK1 to TRAF2 (TNF-α receptor-associated factor) and TRAF6 in the TNF-α and interleukin-1 signaling pathways, respectively (8, 11, 13). Recently, TAB3 has been reported as a new TAK1-binding protein (13). This molecule has a structure similar to TAB2 and functions as a supportive protein of TAB2.

Various alterations of intracellular functions by infecting HTLV-1 and Tax expression result in the onset of ATLL; however, the molecular mechanisms of these alterations are still unclear. The present study investigated whether TAK1 is involved in Tax-dependent NF-κB activation and other signaling pathways in HTLV-1-transformed cells.

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Cell Culture—HTLV-1-transformed cells (19) were maintained in RPMI 1640 supplemented with 10% fetal calf serum, 100 units/ml penicillin, and 100 μg/ml streptomycin at 37 °C in 5% CO₂.

Immunoblotting—Cell lysates, prepared as described previously (6), were resolved by SDS-PAGE and transferred to Immobilon-P nylon membrane (Millipore). The membrane was treated with BlockAce (Dainippon Pharmaceutical Co. Ltd., Suita, Japan) overnight at 4 °C and probed with primary antibodies as described above. Antibodies were detected using horseradish peroxidase-conjugated anti-rabbit, anti-mouse, anti-goat, and anti-sheep IgG (Dako), and visualized with the ECL system (Amersham Biosciences).

Immunoprecipitation—Cell lysates were diluted with an equal volume of dilution buffer (20 mM HEPES, pH 7.7, 2.5 mM MgCl₂, 0.1 mM EDTA, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol, 10 μg/ml aprotinin, and 10 μg/ml leupeptin). After centrifugation, lysates were immunoprecipitated with anti-HA tag antibody (as negative control) or anti-TAB2 antibody or anti-TAB3 antibody on ice for 1.5 h and then rotated with protein G-Sepharose (Amersham Biosciences) at 4 °C for 1.5 h. The Sepharose beads were washed three times with wash buffer (1:1 mixture of whole cell lysate buffer and dilution buffer).

RNA Interference—Cells were electroporated with each siRNA for TAK1, TAB2, Tax, JNK1/2, p38, and firefly luciferase (Luc) using the Amaxa electroporation system. Duplex siRNAs with a two-nucleotide overhang at the 3’-end of the sequence were designed at iGENE Therapeutics and synthesized by Hokkaido System Science Co. The target sequences were as follows: TAK1, UGGCUUAUCUACACUGGA (TAK1–1) and GAGAUGCACUACAAGGAGA (TAK1–2); negative control of TAK1–1, UGGCUUAUCUACCCUGGA (TAK1–m); TAB2, CAGAAUGGAACGACUUCAAAGAGAA; negative control of TAB2–1, UGGCUUAUCUUACACUGGA (TAB2–1) and GAGAUCGACUACAAGGAGA (TAB2–2); TAB3, forward (5′-GCATTCTGGCTGGGTAT-3′) and reverse (5′-GCTGATTTGGCTGTTGA-3′); Tax, ACAAGCGAAUAGAAGAACUCCUCUA; JNK1/2, GCA-UUAAACCCAGACGUGUAAUAAU; JNK2 (MAPK8), GCA-GUUGAGUAGAAAGGAGACACA; JNK2 (MAPK9), CCA-GUGGAGGAAGAGAACAAGCUA; and firefly luciferase (GL2), CGUACGCGGAUACUGCGA.

Real-time RT-PCR—Total RNAs were prepared using the RNeasy Mini kit (Qiagen). First-strand cDNAs were synthesized by SuperScript II reverse transcriptase (Invitrogen). The cDNAs were amplified quantitatively using SYBR Green PCR mix (TaKaRa). The primer sequences were as follows: TAB2, forward (5′-GCATTCTGGCTGGGTAT-3′) and reverse (5′-GCTGATTTGGCTGTTGA-3′); TAB3, forward (5′-TGTAC-TCCATCAACATCTCT-3′) and reverse (5′-TGCTTGTGCT-AACCTCTTCT-3′); and GAPDH, forward (5′-GCTGAAG- GTGCTGTTGACGGATT-3′) and reverse (5′-GATGCC-AAGTTGTGCTGATTGACC-3′). Real-time quantitative RT-PCR was performed using a Prism 7300 sequence detection system (Applied Biosystems). All data were normalized to GAPDH mRNA.

Electrophoretic Mobility Shift Assay—Nuclear extracts were prepared from HuT-102 cells as described previously (21) and probed with 32P-labeled consensus κB and Oct-1 sites. The probes-DNA complexes were separated on 4% PAGE as described previously (21).

Cell Viability Assay—HuT-102 cells cultured for 54 h with 5Z-7-oxozeaenol or IKK inhibitor VI. Cell viability was measured using a Cell Titer-Glo kit (Promega).

RESULTS

Tax-induced Activation of NF-κB and CREB/ATF—We first investigated the relationship between the activation of intracellular signals and Tax expression in HTLV-1 infected cells. As shown in Fig. 1A, Tax expression correlated with activation of the IKK-NF-κB pathway. Constitutive IKK kinase activity correlated with the phosphorylation of p65 at Ser-536 and IκBα at Ser-273/Ser-36 (Fig. 1A). In addition, JNK, p38, CREB, ATF1, and ATF2 were also activated in Tax-expressing T cells (Fig. 1B).

Tax-dependent TAK1 Activation and TAB2 Expression—Although Tax interacts with IκKγ (2), it remains unknown how it activates the IKK complex. Here, we hypothesized that Tax recruits the upstream molecule to activate IKK. TAK1 is a potential candidate for this molecule as it has been shown to be an IKK kinase in several cells including splenic T lymphocytes. We therefore investigated whether Tax could activate TAK1 in HTLV-1-transformed cells. As shown in Fig. 2A, the phosphorylation of TAK1 at Thr-187, a critical site for TAK1 activation, was promoted selectively in Tax-positive cells (Hut-102 and MT-2). Interestingly, in these cells, the expression of TAB2, but not TAB3, increased at the both protein and mRNA levels (Fig. 2B and Oct-1 sites). Real-time quantitative RT-PCR was performed using a Prism 7300 sequence detection system (Applied Biosystems). All data were normalized to GAPDH mRNA.

Electrophoretic Mobility Shift Assay—Nuclear extracts were prepared from HuT-102 cells as described previously (21) and probed with 32P-labeled consensus κB and Oct-1 sites. The pro-
clearly demonstrated that Tax-dependent TAK1 activation is blocked by a specific TAK1 inhibitor (Fig. 3B). These results indicate that TAK1 activation is essential for the activation of MAPKs, but not NF-κB, in Tax-expressed cells. A) HuT-102 cells were treated with 100 nM 7-oxozeaenol for the indicated time. The constitutive phosphorylation of ATF2, but not of CREB and ATF1 (Fig. 4A and B). A JNK-specific inhibitor, SP600125, also inhibited the signal leading to ATF2. We further clarify the role of JNK1 and JNK2 by RNAi and found that JNK1 transduced mainly the TAK1 signal to ATF2 activation (Fig. 4D). These results indicate that TAK1 regulates the activation of ATF2 via JNK1 activation.

**FIGURE 3. TAK1 activation is essential for the activation of MAPKs, but not NF-κB, in Tax-expressed cells.** A) HuT-102 cells were treated with 100 nM 7-oxozeaenol for the indicated time. The constitutive phosphorylation of ATF2, but not of CREB and ATF1 (Fig. 4A and B). A JNK-specific inhibitor, SP600125, also inhibited the signal leading to ATF2. We further clarify the role of JNK1 and JNK2 by RNAi and found that JNK1 transduced mainly the TAK1 signal to ATF2 activation (Fig. 4D). These results indicate that TAK1 regulates the activation of ATF2 via JNK1 activation.

**FIGURE 4. Activation of ATF2 by TAK1 through JNK1.** To characterize the physiological role of activated TAK1 in HTLV-1-transformed cells, we next investigated the effects of TAK1 kinase activity blockade on the CREB/ATF family of transcription factors. Both 7-oxozeaenol and TAK1 siRNA suppressed the constitutive phosphorylation of ATF2, but not of CREB and ATF1 (Fig. 4A and B). A JNK-specific inhibitor, SP600125, also inhibited the signal leading to ATF2. We further clarify the role of JNK1 and JNK2 by RNAi and found that JNK1 transduced mainly the TAK1 signal to ATF2 activation (Fig. 4D). These results indicate that TAK1 regulates the activation of ATF2 via JNK1 activation.

**ACCELERATED PUBLICATION:**

**Tax-mediated Activation of TAK1**

**FIGURE 2. Tax and TAB2 are essential for TAK1 activation in HTLV-1-transformed cells.** A) Cell lysates were immunoprecipitated with anti-TAB2 and anti-TAB3 antibodies. Whole cell lysates and each immunoprecipitated sample were immunoblotted with the indicated antibodies. B) Total RNAs were extracted from each HTLV-1-transformed cell. RNA levels were measured by real-time RT-PCR for TAB2, TAB3, and GAPDH. C) HuT-102 cells were electroporated with each siRNA (5 μM). After incubation at 37 °C for 60 h, cell lysates were extracted and immunoblotted with the indicated antibodies. D) HuT-102 cells were treated with 10 μM 7-oxozeaenol for the indicated time. Cell lysates were immunoprecipitated with anti-TAB2, anti-HA, anti-IKK β antibodies. Each immunoprecipitated sample was immunoblotted with indicated antibodies. D) HuT-102 cells were electroporated with each siRNA (5 μM). After incubation at 37 °C in 5% CO₂ for 60 h, cell lysates were extracted and immunoblotted with the indicated antibodies. E) IKK activity was measured by in vitro kinase assay using purified IKK complex with anti-IKK β antibody. E) HuT-102 cells were electroporated with each siRNA (5 μM). After incubation at 37 °C in 5% CO₂ for 60 h, nuclear extracts were prepared. An electrophoretic mobility shift assay (EMSA) was carried out using 32P-labeled oligonucleotide probes containing consensus κB and Oct-1 sites. F) HuT-102 cells were treated with 7-oxozeaenol (0.1 or 0.9 μM) or 3 μM IKK inhibitor VI for 6 h. After incubation at 37 °C for 60 h, nuclear extracts were prepared. An electrophoretic mobility shift assay (EMSA) was carried out using 32P-labeled oligonucleotide probes containing consensus κB and Oct-1 sites.
of TAB1 with p38α negatively regulates TAK1 kinase activity by phosphorylating TAB1. We therefore hypothesized that the inhibition of p38 promoted the activation of TAK1 by canceling TAB1-dependent feedback inhibition. As expected, p38 inhibitor increased TAK1 activation with decreased TAB1 phosphorylation (Fig. 4F). These results suggest that p38 maintains the level of TAK1 activity by controlling the TAB1-mediated negative feedback mechanism.

**DISCUSSION**

Constitutive activation of NF-κB is a typical pathological alteration in several cancer cells including ATLL cells. We reported previously that IKK phosphorylates p65 at Ser-536 (22). In the present study, enhanced phosphorylation of p65 was observed in Tax-positive cells, suggesting that p65 phosphorylation will be a useful marker for detecting the constitutive activation of NF-κB in cancer cells. We also found that TAK1 is constitutively activated through Tax-mediated overexpression of TAB2 (Fig. 2A). TAK1 has been shown to play a critical role in NF-κB activation in response to various extracellular stimuli including T cell receptor activation (5, 7, 9–11, 15, 23). Therefore, we hypothesized that Tax-dependent activation of TAK1 might induce IKK activation; however, our data did not support this hypothesis (Fig. 2C). Wu and Sun (24) recently reported that TAK1 is involved in Tax-induced activation of NF-κB; however, no direct evidence of the role of TAK1 in Tax induction of NF-κB in HTLV-1-transformed cells was shown. In contrast, this led to the conclusion of direct blockade of TAK1 kinase activity using both chemical inhibitor and siRNA in HTLV-1 transformed cells. They also showed that TAK1 associates with Tax-IKK complex in SLB-1 cells (Tax-positive HTLV-1-transformed cells). We also observed constitutive activation of TAK1 in the cell line (data not shown); however, the association of TAK1 with the Tax-IKK complex could not be detected in HuT-102 cells (Fig. 3C). Consistent with our data, Ghoda et al. (25) reported that Tax is not able to induce IKK phosphorylation in TAK1−/− MEFs. Further study will be necessary to settle this issue; however, we currently believe that Tax-dependent IKK activation is regulated by a factor other than TAK1. Recently, protein phosphatase 2A has been reported as a candidate for this factor (26).

The JNK pathway has been widely accepted as another main signal triggered by activated TAK1. It should be noted that TAK1 is essential for activation of the JNK-ATF2 pathway in HTLV-1-infected cells. RNAi experiment also revealed that JNK1, but not JNK2, is essential for activation of ATF2. In addition, persistent activation of p38α negatively regulated the TAK1-JNK1-ATF2 pathway by phosphorylating TAB1. Moreover, the Wnt/β-catenin pathway is known as a target for TAK1 (27, 28); however, TAK1 inhibitor had no inhibitory effect on the stable expression of β-catenin in HTLV-1-infected cells (data not shown). Collectively, we claim that the constitutive activation of TAK1 led to the activation of stress-activated MAPKs but not NF-κB.

It has been reported that the expressions of various genes, including cIAP2, CCR6, CCR4, CXCR4, and STAT5, are up-regulated in Tax-positive ATLL cells compared with Tax-negative T cells. We therefore assessed the effects of TAK1 knockdown on the expression of these genes; however, no inhibitory effect was observed (data not shown). In contrast, knockdown of NF-κB p65 resulted in the down-regulation of cIAP2 gene expression (data not shown). This was correlated with the fact that IKK inhibitor, but not TAK1 inhibitor, induced cell death (Fig. 3E). Microarray analysis will help our understanding of the physiological function of activated TAK1 in HTLV-1-transformed cells.

Another important finding in the present study is that TAB2, but not TAB3, is overexpressed in a Tax-dependent fashion. TAB2 has been characterized as an adaptor protein that regulates the activation of TAK1. Interestingly, it has recently been reported that TAB2 localizes in the nucleus and is able to associate with a transcriptional co-repressor NcoR, an epidermal growth factor receptor family (ErbB4), and nuclear receptors such as androgen receptor (29, 30). These reports suggest that TAB2 has several potential physiological functions apart from TAK1 activation. Therefore, further study from the viewpoint...
of TAB2 overexpression, including analysis of the transcriptional mechanism of TAB2 expression and a search for its associate proteins in HTLV-1-infected cells, will shed light on the pathophysiological importance of our findings. In addition, it is interesting to speculate whether TAB2 is overexpressed in other cancer cells.

In summary, we have provided a new insight into the pathophysiological function of TAK1 in HTLV-1-infected T cells. TAK1 has also been shown to be an oncoprotein component of the Epstein-Barr virus latent membrane protein 1 complex (31, 32). These findings altogether raise the possibility that TAK1 is a key molecule in virus-related oncogenesis; however, virus infection and oncoproteins dramatically change the intracellular environment. Further basic and clinical investigations will be essential in exploring this possibility.

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