Human T-cell leukemia virus type 1 Tax protein stimulates the interferon-responsive enhancer element via NF-κB activity[1]

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Abstract Gene expression in Rat-1 fibroblast cells transformed by Tax from human T-cell leukemia virus type 1 was studied using the reverse transcriptase polymerase chain reaction differential display technique. The analysis revealed eight genes that were upregulated and one gene that was suppressed in Tax-transformed cells. Interestingly, at least four of the upregulated genes were interferon-stimulated genes. Promoter analysis of the 2′,5′-oligoadenylate synthetase gene, which was activated in both Tax-transformed Rat-1 cells and primary adult T-cell leukemia cells, demonstrated that Tax indirectly activates its interferon-responsive enhancer element in a nuclear factor-κB pathway-dependent manner, indicating a close association of interferon signaling with the transformation by Tax.

Key words: Human T-cell leukemia virus type 1; Tax; Transformation; Nuclear factor-κB; Interferon responsive element; 2′,5′-Oligoadenylate synthetase

1. Introduction

Human T-cell leukemia virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia (ATL) [1,2]. The viral protein Tax is thought to play a critical role in leukemogenesis because of its transforming activity in various experimental systems: the immortalization of rat embryo fibroblasts (REF) and human T-lymphocytes [3], ras-dependent focus formation of REF, and anchorage-independent growth of Rat-1 cells.

Tax transactivates its own long terminal repeat and various cellular genes, including cytokines/chemokines (interleukin (IL) 1α, IL-2, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, interferon-inducible protein-10 (IP-10)), their receptors (the a chain of the IL-2 receptor (IL-2R), IL-15R, and CXCR4), nuclear transcriptional factors (c-*fos*, c-*jun*, interferon regulatory factor (IRF) 4), cytoplasmic signal mediator (*lyn*), apoptosis inhibitor (Bcl-X_L), and G1-cyclins. Conversely, Tax represses the transcription of some cellular genes. Analyses of target DNA sequences revealed that Tax activates at least three enhancer elements: those that bind to the cyclic AMP-responsive element binding factor (CREB/ATF), nuclear factor (NF) κB, and serum-responsive factor (SRF). The transcriptional suppression mediated via E-box binding protein and functional inactivation of the p53 tumor suppressor gene product were attributed to the sequestration of a transcriptional co-factor, CBP/p300, by Tax protein [4].

Interestingly, using a set of enhancer-specific Tax mutants [5], it was shown that distinct enhancer pathways are involved in at least the latter two transformation phenotypes. The NF-κB pathway is required for the anchorage-independent growth of Rat-1 cells [6], while SRF activity is necessary in focus formation of REF [7]. To immortalize T-cells, the inactivation of INK4a, a tumor suppressor gene product that inhibits CDK4/6 kinase activity, via a direct interaction with Tax in an NF-κB-dependent manner, has been implicated [8], although some results do not support the requirement for the NF-κB pathway [9]. These results indicate that multiple activities of Tax are involved in establishing the transformed phenotype of HTLV-1-infected T-cells in ATL patients.

The Rel/NF-κB family of transcription factors regulates gene expression via promoters or enhancers containing the κB binding site (GGGRNNYYCC, where R is a purine, Y is a pyrimidine, and N is any nucleotide). Rel/NF-κB proteins coordinate the expression of genes involved in natural and acquired immunity, and also control cell growth and apoptosis. In addition, altered regulation of Rel/NF-κB activity has been linked to several pathological processes, including oncogenesis. While Tax protein leads to persistent NF-κB activity via the activation of IκB kinase kinases in HTLV-1-infected T-cells [10], continuous NF-κB activation in primary ATL cells occurs via a mechanism that is independent of Tax [11]. Therefore, NF-κB activity seems to be involved in both the development and maintenance of leukemogenesis caused by HTLV-1.

Although Tax function related to NF-κB activation is responsible for Rat-1 cell transformation, its mechanism is still totally unknown. To address this question, we searched for

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[1] The nucleotide sequences for rat 2,5-oligoadenylate synthetase-2, CyCAP/90K/MAC-2 binding protein, schlafen-4, and calpain-6 have been submitted to GenBank database under accession numbers AF068268, AF065438, AF168795, and AF067793, respectively.

Abbreviations: HTLV-1, human T-cell leukemia virus type 1; ATL, adult T-cell leukemia; RT-PCR, reverse transcriptase polymerase chain reaction; NF-κB, nuclear factor-κB; 2,5-OAS, 2′,5′-oligoadenylate synthetase; ISG, interferon-stimulated genes; ISRE, interferon stimulation response element; PBMC, peripheral blood mononuclear cell

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genes that are modulated by Tax in the course of transformation using the reverse transcriptase polymerase chain reaction (RT-PCR) differential display technique [12]. As a result, we found that Tax expression in Rat-1 cells leads to transcriptional activation of a series of interferon-stimulated genes (ISGs) and promoter analysis of the 2′,5′-oligoadenylate synthetase (2,5-OAS) gene, which was activated in both Tax-transformed Rat-1 cells and primary ATL cells, revealed that Tax activates its interferon-responsive enhancer element in a manner dependent on the NF-κB pathway. These results suggest a close association of interferon signaling with the transformed phenotype.

2. Materials and methods

2.1. Cell culture and Tax expression

Rat-1 and HeLa cells were grown in Dulbecco's modified Eagle's medium supplemented with 5% fetal calf serum. To obtain Tax-transformed Rat-1 cells, 10^5 cells were infected with 10^2–10^3 cfu of MLV-based recombinant retrovirus expressing Tax (RTaxbsr [13]) and its mutants, and selected for 10 days in 10 ml of culture medium containing 10 μg/ml blasticidin S (Kakenseiyaku, Tokyo, Japan). Recombinant retroviruses were produced by transfecting retroviral vector DNA, pRTaxbsr [13], or its derivatives, into BOSC23 packaging cells using LipofectAmine (Gibco BRL, Grand Island, NY, USA). Human interferon-α was obtained from Sumitomo Pharmaceutical (Takarazuka, Japan).

2.2. RT-PCR differential display analysis and cDNA isolation

Differential display of total RNA was performed as previously described [12]. Briefly, 5 μg of total RNA prepared from a pool of about 100 cell clones transformed with wild-type Tax or its mutant forms were reverse-transcribed using SuperScript-II (Gibco BRL) with one of four degenerate anchored oligo-dT primers (T_{12}VG, T_{12}VA, T_{12}VT, and T_{12}VC, where V may be G, A, or C), containing 12 T nucleotides. The single-stranded cDNA was then used in PCR with one of these four 3′ primers and one of 20 possible arbitrary random decamers (OPA-1 to OPA-20) as 5′ primers. The PCR products were resolved on denaturing 6% polyacrylamide gels to obtain a profile of the RNA population. The band pattern obtained with Tax-transformed Rat-1 was compared with that obtained with Rat-1 cells transformed with empty retrovector and the PCR products representing mRNA whose expression was altered by Tax transformation were excised from the acrylamide gel, re-amplified with the same primers, and cloned into pGEM-T Easy vector (Promega, Madison, WI, USA).

To isolate the full-length cDNA, λZAP cDNA libraries prepared with poly(A)$^+$ mRNA from Rat-1 or Tax-transduced Rat-1 cells were screened using ^{32}P-labeled cDNA fragments obtained in the differential display analysis. The nucleotide sequences of these cDNAs were determined and analyzed by searching for homologous sequences in GenBank using the search program BLAST.

2.3. Northern and RT-PCR analysis

Total RNA (10 μg) prepared from Rat-1 cells transformed with Tax and its mutants was separated in a 1% agarose gel containing 10% formalin in 1×MOPS, transferred to a Hybond-N$^+$ membrane (Amersham Pharmacia Biotech, Buckinghamshire, UK), and then probed with a ^{32}P-labeled cDNA fragment.

For RT-PCR, cDNA was synthesized from 5 μg of total RNA using SuperScript-II reverse transcriptase and an oligo-dT_{12-18} primer (Amersham). The same amounts of cDNA were subjected to 30 cycles of PCR in 20 μl of reaction buffer containing 10 pmol of each primer. The individual cycles consisted of 20 s at 98°C and 2 min at 68°C; the sequences of oligonucleotide primers were as follows: for rat 2,5-OAS-1, 5′-GGAGATACATTCGGAGATGAGGAT-3′ and 5′-CCTGGTCATGCATCCTGCTGTGAA-3′; for rat 2,5-OAS-2, 5′-AGATTAACTAAGTTCAACACAGCC-3′ and 5′-ACTTTGGGCTATACAGAATGCTTC-3′; for rat IP-10, 5′-CTGTCGTTCTCTGCCTC-GTGCTGC-3′ and 5′-CCGTCTCTCTGCTGTCCATCGGTC-3′; for human 2,5-OAS, 5′-CTCATCCGCCTAGTCAAGCACTGG-3′ and 5′-AGCTATATGCTCAAGCTTCATGG-3′; for human IP-10, 5′-TGATTTGCTGCCTTATCTTTCTGA-3′ and 5′-CAGCCTCTGTGTGGTCCATCCTTG-3′; for rat and human β-actin, 5′-GTGTTGAAGGTCTCAAACATGATCTGGGTC-3′ and 5′-CAAGATCATTGCTCCTCCTGAGCGCAAGTA-3′.

2.4. Luciferase assay

Luciferase reporter plasmids were constructed by inserting human 2,5-OAS promoter fragments, which were isolated by PCR of HeLa cell genomic DNA, into the multi-cloning site of pGL3-basic plasmid. Expression plasmids for Tax and NF-κB, pCGTax and pCGp65 have been described previously [14]. The human IRF-3 coding region was amplified by PCR, sequence-verified and subcloned into an empty vector resulting in pCG-IRF-3. The expression plasmid for the dominant negative form of NF-κB [15], pCGDNκB, was constructed by inserting a 1.1-kb *Pst*I-*Xba*I fragment of NF-κB p105 precursor cDNA into the pCG vector. The reporter plasmids (50 ng) were transfected to HeLa cells grown in 24-well multi-well dishes with 50 ng of a control vector, pRL-RSV (Promega), and 20 ng each of effector plasmids by using LipofectAmine (Gibco BRL). The cell lysates were prepared after 24 h and the luciferase assay was performed according to the manufacturer's protocol for the Dual-Luciferase Reporter Assay System (Promega).

3. Results

3.1. Genes differentially expressed in Tax-transformed Rat-1 cells

About 1000 transcripts were analyzed by RT-PCR differential display using combinations of 20 different arbitrary primers and four anchor primers. Eighty-seven cDNA fragments that were differentially expressed between mock- and Tax-transformed Rat-1 cells were isolated from gels and subcloned into vector plasmid. Using these fragments as probes, the enhanced or suppressed expression of differentially expressed genes was analyzed by Northern blot analysis. Since most cDNA bands in the differential display consisted of multiple fragments encoding 3′-non-coding regions, which exhibited relatively low affinity and specificity in the hybridization, for only nine cDNA fragments could the differential expression be successfully confirmed. As shown in Fig. 1A, eight genes were concluded to be upregulated in Tax-transformed Rat-1 cells and the transcription of one gene was decreased in these cells.

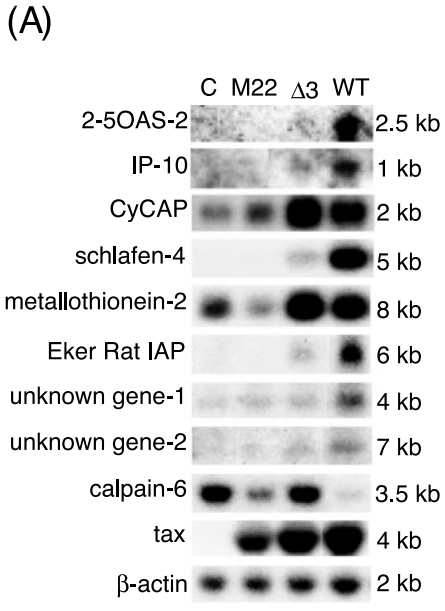
Longer or full-length cDNAs were further screened by the same probes in cDNA libraries of Rat-1 or Tax-transduced Rat-1 cells. The nucleotide sequences of these cDNAs were determined and the identity of each clone was analyzed in a BLAST homology search. The BLAST search revealed that these genes included rat orthologues of a subtype of 2,5-OAS (we named and deposited it as rat 2,5-OAS-2, but have recently found it most homologous to murine OAS-1b [16]), IP-10 [17], CyCAP/90K/MAC-2 binding protein [18], schlafen-4 [19], metallothionein-2, intra-cisternal A particle [20], and calpain-6 [21].

3.2. Activation of genes in Tax-transformed cells involves the NF-κB pathway

The expression of these genes was also analyzed in Rat-1 cells that were transduced with various Tax mutants. Mutant Δ3, which lacks three amino acids at the amino-terminus end, activates the NF-κB pathway, but fails to activate the CREB/ATF and SRF pathways [22]. Conversely, mutant M22, which has a Thr-Leu to Ala-Ser substitution at the 130th amino acid, cannot activate the NF-κB pathway, but retains the ability to activate the CREB/ATF and SRF pathways [5]. Northern analysis of transcripts in cells transformed with

Tax mutants revealed that six out of the eight upregulated genes appeared to be activated in the Δ3 transformant, but not in the M22 transformant, although the magnitude of enhancement in the Δ3 mutant was minimal for most of these genes (Fig. 1A). The activation of 2,5-OAS-2 and IP-10 genes in the Δ3 transformant was confirmed by RT-PCR as shown in Fig. 1B. The results suggest that these genes are activated by Tax at least partly in an NF-κB-dependent manner. In the full activation of these genes, the CREB/ATF and SRF pathways or some unknown pathway could be synergistically involved with the NF-κB pathway.

Two of the upregulated genes did not match any known genes and appeared to be activated little by Δ3 and M22 mutants. These genes were not analyzed further because of lack of the NF-κB dependence, which is associated with



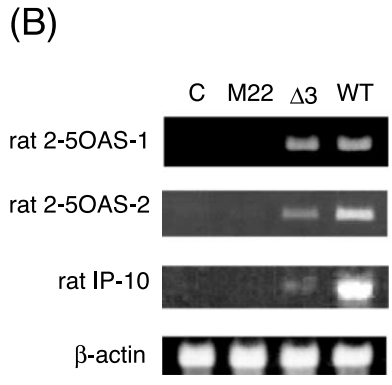


Fig. 1. Expression of modulated genes in Tax-transformed Rat-1 cells. A: Total RNAs (10 μg/lane) from Rat-1 cells transformed with Tax and its mutant forms, M22 and Δ3, on a transfer membrane were hybridized with a ^{32}P-labeled probe for the respective cDNAs. The first lane contained RNA from Rat-1 cells transduced with an empty retrovector. Approximate lengths of hybridized mRNAs are presented. B: Activation of mRNA expressions from rat 2,5-OAS-1, 2,5-OAS-2 and IP-10 genes in Tax-transformed Rat-1 cells was demonstrated by RT-PCR. Expression of β-actin mRNA is presented as a control in both A and B.

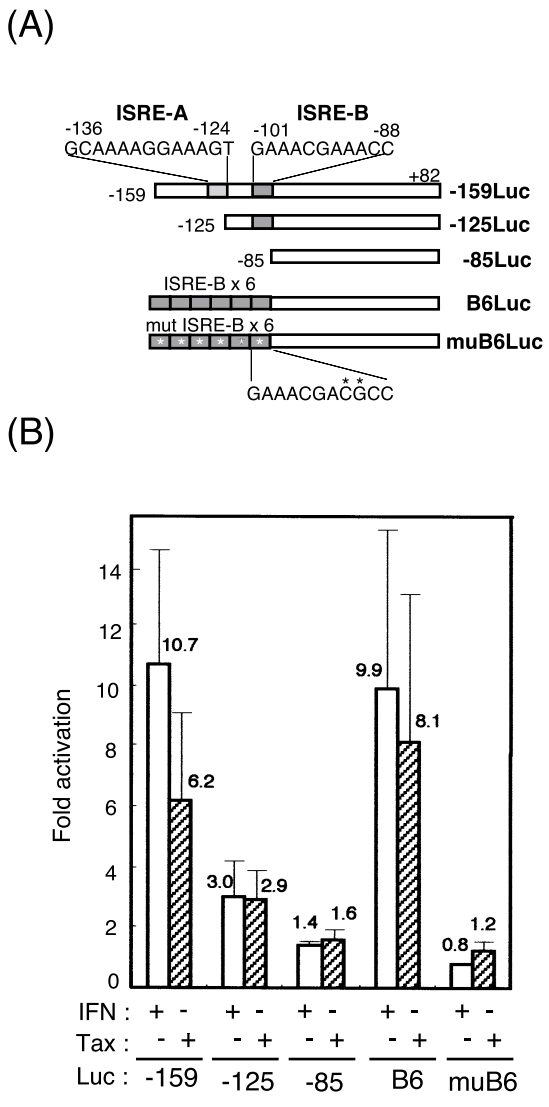


Fig. 2. Transcriptional activation of 2,5-OAS promoter by IFN-α and Tax. A: Structures of human 2,5-OAS reporter plasmids and nucleotide sequences of ISRE-B and its mutant. B: Both interferon-α treatment (100 U/ml, white bar) and Tax expression (hatched bar) stimulated ISRE of 2,5-OAS promoter in HeLa cells. Luciferase activities were normalized based on the *Renilla* luciferase activity from pRSV-RL and are shown as fold activation to that of control transfection with empty expression vector. Mean values and standard errors for four independent assays are presented.

Rat-1 transformation. Of interest, no gene was upregulated by M22, indicating that few genes are activated solely via the CREB/ATF and SRF pathways in Tax-transformed cells. By contrast, suppressed expression of the calpain-6 gene was observed in cells transformed with wild-type Tax and partially in those with M22 mutants (Fig. 1A).

3.3. *Interferon-inducible genes were activated in Tax-transformed Rat-1 cells*

Of the six upregulated genes, four were previously reported to be interferon-stimulated genes (ISGs). IP-10 is a CXC chemokine that has been cloned as a protein induced by interferon-γ [17]. CyCAP (cyclophilin C-associated protein [18], also known as 90K/MAC-2 binding protein, a glycoprotein belonging to the scavenger receptor family) has been identified as an intracellular ligand of cyclophilin C and is induced by

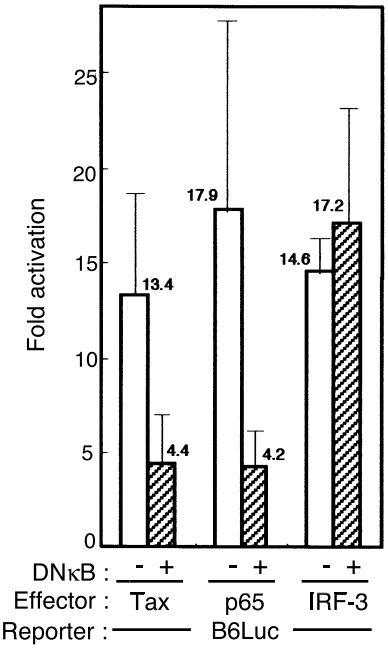


Fig. 3. Activation of ISRE by Tax and NF-κB. B6Luc reporter plasmid (50 ng) was transfected to HeLa cells with expression plasmids (20 ng) for Tax, p65, and IRF-3 in the presence (+) or absence (−) of the dominant negative NF-κB expressor (20 ng). Luciferase activities were measured and presented as in Fig. 2.

the action of interferon [23]. Genes for metallothionein-1 and -2 are also interferon-responsive [24].

Rat 2,5-OAS-2 is a gene related to 2,5-OAS-1, which is one of the best-characterized ISGs. Therefore, we examined the expression of rat 2,5-OAS-1 in Tax-transformed Rat-1 cells by RT-PCR and demonstrated that activation of its gene is associated with Tax expression in an NF-κB-dependent manner (Fig. 1B).

3.4. Tax-activated interferon-responsive element in Rat-1 cells

We then asked whether interferon stimulation and Tax activation share a pathway in the transactivation of interferon-inducible genes. To answer this question, a luciferase reporter plasmid was constructed using the interferon-responsive promoter fragment from the human 2,5-OAS gene, in which the interferon response has been extensively studied [25] (Fig. 2A). When HeLa cells were transfected with the reporter plasmid containing a promoter fragment (−159 to +82) and treated with human interferon-α, luciferase expression was enhanced about 10-fold. By contrast, on deleting the nucleotide sequence harboring two interferon response elements (ISRE-A and ISRE-B, Fig. 2A), the interferon response was lost (−85Luc, Fig. 2B). When the Tax expression plasmid was co-transfected, the reporter plasmids with two or one of the 2,5-OAS enhancer elements, −159Luc and −125Luc, but not the enhancer-less reporter, were activated (6.2- and 2.9-fold, respectively) by Tax to a similar extent as with interferon stimulus (10.7- and 3.0-fold, respectively). In addition, the reporter plasmid containing a hexamer of the ISRE-B fragment on the enhancer-less promoter was activated by Tax co-transfection as well as by interferon stimulation (B6Luc, Fig. 2B). Introduction of a mutation in the ISRE-B sequence abolished both forms of activation (muB6Luc, Fig. 2B), confirming the involvement of ISRE in Tax activation.

3.5. NF-κB-dependent activation of ISRE

All of the ISGs upregulated in Tax-transformed cells seemed to be activated in an NF-κB-dependent manner. Therefore, we examined whether NF-κB transcription factors were actually involved in the transactivation of ISGs via the ISRE sequence.

As shown in Fig. 3, overexpression of the p65 subunit of the NF-κB molecule resulted in the activation of ISRE. Furthermore, a dominant negative form of the NF-κB molecule [15], which inhibits the binding of Rel/NF-κB proteins to DNA, was co-transfected, and both the Tax- and NF-κB-dependent stimulations of the ISRE reporter were diminished, whereas the activation of ISRE by the over-expression of IRF-3, which plays a prominent role in the interferon induction via ISRE, was not affected. Since there is no evidence that NF-κB molecules directly associate with the ISRE sequence, it is more likely that some other factor(s), which may be induced by the function of NF-κB, is involved in the modulation caused by the ISRE sequence.

3.6. 2,5-OAS activation in peripheral blood lymphocytes from ATL patients

Although the in vivo expression of HTLV-1 including the Tax gene in primary ATL cells was suppressed, continuous NF-κB activation was observed via a mechanism that is independent of Tax, suggesting that NF-κB activity is involved in both the development and maintenance of leukemogenesis caused by HTLV-1. Therefore, it was of interest whether the induction of ISGs was common to primary ATL cells. To assess this possibility, expressions of 2,5-OAS and IP-10 were analyzed using an RT-PCR procedure using total RNA prepared from peripheral blood mononuclear cells (PBMCs) from ATL patients.

As shown in Fig. 4, transcription from the human 2,5-OAS gene was upregulated in all cases of ATL leukemic cells tested, whereas normal PBMC exhibited little expression. Therefore, 2,5-OAS is also activated in primary ATL cells, indicating the ISRE activation in ATL cells. Combined with the result of ISRE activation by NF-κB signaling in the 2,5-OAS promoter, a close association of interferon signaling with the transforming phenotype of ATL cells is strongly suggested.

However, although three out of seven ATL cases exhibited the upregulation of the IP-10 gene, the remainder of the ATL cells expressed a similar or even decreased level of transcription when compared with that in normal PBMC. These results indicate that NF-κB activity may not necessarily result in the induction of all ISGs, which is probably dependent on the configuration of enhancer elements and the cell type.

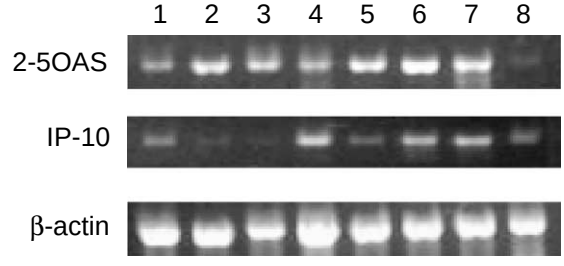


Fig. 4. Expressions of human 2,5-OAS and IP-10 genes in ATL leukemic cells. 0.1 μg of total RNA from PBMCs of ATL patients (lanes 1–7) and a healthy donor (lane 8) was reverse-transcribed and PCR-amplified with primer pairs for human 2,5-OAS (upper panel), IP-10 (middle panel) and β-actin (lower panel).

4. Discussion

Using an RT-PCR differential display technique, we identified six genes whose expression was specifically modulated in Tax-transformed Rat-1 cells, and at least four of them were found to be ISGs. Promoter analysis of one of the activated genes, 2,5-OAS, revealed that Tax activated its ISRE in an NF-κB pathway-dependent manner. These results strongly suggest that some other factor(s), which may be induced by the function of NF-κB, is involved in the modulation caused by the ISRE sequence in Tax-transformed Rat-1 cells.

There is increasing evidence of a close link between interferon signaling and NF-κB activity. Activation of cells by either double-stranded RNA or bacterial lipopolysaccharide (LPS) via Toll-like receptor (TLR)-3 and TLR-4, respectively, which leads to the induction of type I interferons and various ISGs, involves activation of both IRFs and NF-κB [26]. Using LPS-stimulated human umbilical vein endothelial cells, Liu et al. found evidence of the direct involvement of NF-κB in the induction of IRF-1 [27]. The induction and activation of IRF-7 by Epstein–Barr virus (EBV) latent membrane protein 1 is also attributed to the NF-κB signaling pathway [28], and IRF-7 has been suggested to have a role in latent EBV infection. Therefore, the induction of ISGs by NF-κB in HTLV-1-infected cells might help to sustain the lower expression of viral genes, allowing them to escape the host immune system [29].

In terms of cellular transformation, IRF-4, which is abundant in HTLV-1-infected T-cells [30,31], is of the most interest, because v-Rel transformation of chick embryo fibroblasts has recently been demonstrated to involve the induction of IRF-4 as well as the expression of several ISGs [32]. Since the suppression of IRF-4 expression by antisense RNA reversed the transformed phenotype of the fibroblast, the authors suggested that IRF-4 facilitates transformation by decreasing the anti-proliferative effects of ISGs. Therefore, IRF-4 may also be involved in the NF-κB-dependent transformation of Rat-1 cells by Tax. In fact, our preliminary experiment demonstrated that over-expression of IRF-4 did activate the reporter plasmid with the ISRE sequence of the 2,5-OAS gene (data not shown). Furthermore, a role for IRF-4 in the transcriptional regulation of IL-15 receptor α by HTLV-1 Tax has also been demonstrated recently [33]. Combined with our result that expression of the 2,5-OAS gene was observed in primary ATL cells, in which NF-κB activity is consistently augmented, it would be possible that IRF-4 is involved in the transforming phenotype of ATL cells.

The biological significance of the induction of ISGs in the course of cellular transformation is unclear and inconsistent activation of the IP-10 gene in primary ATL cells rather argues against this possibility. However, since accumulating evidence demonstrates that several IRFs act differently on ISREs in a promoter-specific manner, the induction of a discrete set of ISGs could be involved in the transformed phenotype and further study of such genes should elucidate a close link between Rel/NF-κB activity and interferon signaling in cellular transformation.

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References

[1] Poiesz, B.J., Ruscetti, F.W., Gazdar, A.F., Bunn, P.A., Minna, J.D. and Gallo, R.C. (1980) Proc. Natl. Acad. Sci. USA 77, 7415–7419.
[2] Yoshida, M., Seiki, M., Yamaguchi, K. and Takatsuki, K. (1984) Proc. Natl. Acad. Sci. USA 81, 2534–2537.
[3] Akagi, T., Ono, H., Nyunoya, H. and Shimotohno, K. (1997) Oncogene 14, 2071–2078.
[4] Suzuki, T., Uchida-Toita, M. and Yoshida, M. (1999) Oncogene 18, 4137–4143.
[5] Smith, M.R. and Greene, W.C. (1991) J. Clin. Invest. 88, 1038–1042.
[6] Yamaoka, S., Inoue, H., Sakurai, M., Sugiyama, T., Hazama, M., Yamada, T. and Hatanaka, M. (1996) EMBO J. 15, 873–887.
[7] Matsumoto, K., Shibata, H., Fujisawa, J.I., Inoue, H., Hakura, A., Tsukahara, T. and Fujii, M. (1997) J. Virol. 71, 4445–4451.
[8] Suzuki, T., Kitao, S., Matsushime, H. and Yoshida, M. (1996) EMBO J. 15, 1607–1614.
[9] Rosin, O., Koch, C., Schmitt, I., Semmes, O.J., Jeang, K.T. and Grassmann, R. (1998) J. Biol. Chem. 273, 6698–6703.
[10] Sun, S.C. and Ballard, D.W. (1999) Oncogene 18, 6948–6958.
[11] Mori, N., Fujii, M., Ikeda, S., Yamada, Y., Tomonaga, M., Ballard, D.W. and Yamamoto, N. (1999) Blood 93, 2360–2368.
[12] Ito, T., Kito, K., Adati, N., Mitsui, Y., Hagiwara, H. and Sakaki, Y. (1994) FEBS Lett. 351, 231–236.
[13] Furuta, R.A., Sugiura, K., Kawakita, S., Inada, T., Ikehara, S., Matsuda, T. and Fujisawa, J. (2002) J. Virol. 76, 2703–2713.
[14] Hirai, H., Suzuki, T., Fujisawa, J., Inoue, J. and Yoshida, M. (1994) Proc. Natl. Acad. Sci. USA 91, 3584–3588.
[15] Logeat, F., Israel, N., Ten, R., Blank, V., Le Bail, O., Kourilsky, P. and Israel, A. (1991) EMBO J. 10, 1827–1832.
[16] Perelygin, A.A., Scherbik, S.V., Zhulin, I.B., Stockman, B.M., Li, Y. and Brinton, M.A. (2002) Proc. Natl. Acad. Sci. USA 99, 9322–9327.
[17] Luster, A.D., Unkeless, J.C. and Ravetch, J.V. (1985) Nature 315, 672–676.
[18] Friedman, J., Trahey, M. and Weissman, I. (1993) Proc. Natl. Acad. Sci. USA 90, 6815–6819.
[19] Schwarz, D.A., Katayama, C.D. and Hedrick, S.M. (1998) Immunity 9, 657–668.
[20] Xiao, G.H., Jin, F. and Yeung, R.S. (1995) Oncogene 11, 81–87.
[21] Matena, K., Boehm, T. and Dear, N. (1998) Genomics 48, 117–120.
[22] Hirai, H., Fujisawa, J., Suzuki, T., Ueda, K., Muramatsu, M., Tsuboi, A., Arai, N. and Yoshida, M. (1992) Oncogene 7, 1737–1742.
[23] Trahey, M. and Weissman, I.L. (1999) Proc. Natl. Acad. Sci. USA 96, 3006–3011.
[24] Giralt, M., Carrasco, J., Penkowa, M., Morcillo, M.A., Santamaria, J., Campbell, I.L. and Hidalgo, J. (2001) Exp. Neurol. 168, 334–346.
[25] Cohen, B., Peretz, D., Vaiman, D., Benech, P. and Chebath, J. (1988) EMBO J. 7, 1411–1419.
[26] Alexopoulou, L., Holt, A.C., Medzhitov, R. and Flavell, R.A. (2001) Nature 413, 732–738.
[27] Liu, L., Paul, A., MacKenzie, C.J., Bryant, C., Graham, A. and Plevin, R. (2001) Br. J. Pharmacol. 134, 1629–1638.
[28] Zhang, L., Wu, L., Hong, K. and Pagano, J.S. (2001) J. Virol. 75, 12393–12401.
[29] Hanon, E., Hall, S., Taylor, G.P., Saito, M., Davis, R., Tanaka, Y., Usuku, K., Osame, M. and Weber, J.N. (2000) Blood 95, 1386–1392.
[30] Yamagata, T., Nishida, J., Tanaka, S., Sakai, R., Mitani, K., Yoshida, M., Taniguchi, T., Yazaki, Y. and Hirai, H. (1996) Mol. Cell. Biol. 16, 1283–1294.
[31] Sharma, S., Manane, Y., Grandvaux, N., Bartlett, J., Petropoulos, L., Lin, R. and Hiscott, J. (2000) AIDS Res. Hum. Retroviruses 16, 1613–1622.
[32] Hrdlickova, R., Nehyba, J. and Bose Jr., H.R. (2001) Mol. Cell. Biol. 21, 6369–6386.
[33] Mariner, J.M., Mamane, Y., Hiscott, J., Waldmann, T.A. and Azimi, N. (2002) J. Immunol. 168, 5667–5674.