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Transcriptional activation of long terminal repeat of bovine leukemia virus by bovine heat shock factor 1

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ABSTRACT

Bovine leukemia virus (BLV) causes enzootic bovine leukosis (EBL). The BLV genome encodes Tax protein, a transcriptional activator of viral gene expression that binds to the BLV long terminal repeat (LTR). Heat shock factor 1 (HSF1) is a known regulator of the heat shock response proteins, including heat shock proteins. In the present study, the BLV LTR was investigated for interaction of heat shock element (HSE) with HSF1 and the viral Tax protein. It could be confirmed that a functional HSE is well conserved in different BLV strains. The LTR transcriptional activity, as measured by luciferase reporter assay, was upregulated by bovine HSF1 - without Tax expression - in feline CC81 cells. The HSF1 activated LTR transcription by binding to the HSE. LTR-activation was lost upon HSE removal from the LTR and upon expression of a mutant HSF1 lacking the DNA-binding domain. We conclude that BLV LTR is activated to a basal level by host transcriptional factor HSF1, but without Tax protein involvement.

1. Introduction

Bovine leukemia virus (BLV) belongs to the genus *Deltaretrovirus* of the family *Retroviridae* and causes enzootic bovine leukosis (EBL) after a long latent period (Burny et al., 1988). The BLV transcriptional promoter is located in the long terminal repeat (LTR) comprising the U3, R, and U5 regions. The U3 region contains important promoters including Tax response element (TxRE) and glucocorticoid response element (GRE). Tax protein is one of the regulatory proteins encoded in the pX region of the BLV genome and binds to three 21-bp repeats of TxRE in the U3 region of the 5´ LTR (Derse, 1987, 1988; Willems et al., 1987). BLV Tax protein is required for efficient BLV transcription (Derse, 1987; Katoh et al., 1989; Willems et al., 1998). However, Tax protein and virus transcription are undetectable in the latent stage of BLV infection, and the initial transcription of the proviral BLV genes after the infection of a cell is considered independent of Tax protein (Merimi et al., 2007; Van den Broeke et al., 1988).

Heat shock factors (HSFs) are regulators of many heat shock proteins (HSPs) in *Drosophila* and *Saccharomyces* (Clos et al., 1990; Wiederrecht et al., 1988). In mammals, Heat shock factor 1 (HSF1) regulates transcriptional responses against heat shock (Rabindran et al., 1991; Sarge et al., 1991). HSF1 binds to a heat shock element (HSE), which is a DNA sequence motif encoded by two or three inverted repeats of a consensus motif (5´-nGAAn-3´) (Wu, 1995). HSF1 is considered not only a heat shock regulator but also a genome-wide transcriptional regulator in mammalian cells (Trinklein et al., 2004). Several studies suggest that the LTR of human immunodeficiency virus 1 (HIV-1) has an HSE sequence, and the LTR is activated in response to HSF1 (Hashimoto et al., 1996; Ignatenko and Gerner, 2003; Re et al., 1989). However, heat shock activation of LTR-mediated transcription in BLV has not been thoroughly investigated. Because host cell factors were assumed to be involved in BLV LTR activity, in the present study, we examined whether HSF1 was able to regulate the transcriptional activation or repression of the LTR of BLV with and without BLV Tax protein.

2. Materials and methods

2.1. Blood and tissue samples

Leukocytes were collected from clinically asymptomatic cattle to isolate the HSF-1 gene. It was confirmed that the cow was not infected with BLV by agar gel immunodiffusion tests (Kono et al., 1982) and polymerase chain reaction (PCR) (Fechner et al., 1996). Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes from the tail vein of cattle. After erythrocyte lysis by mixing with two volumes of

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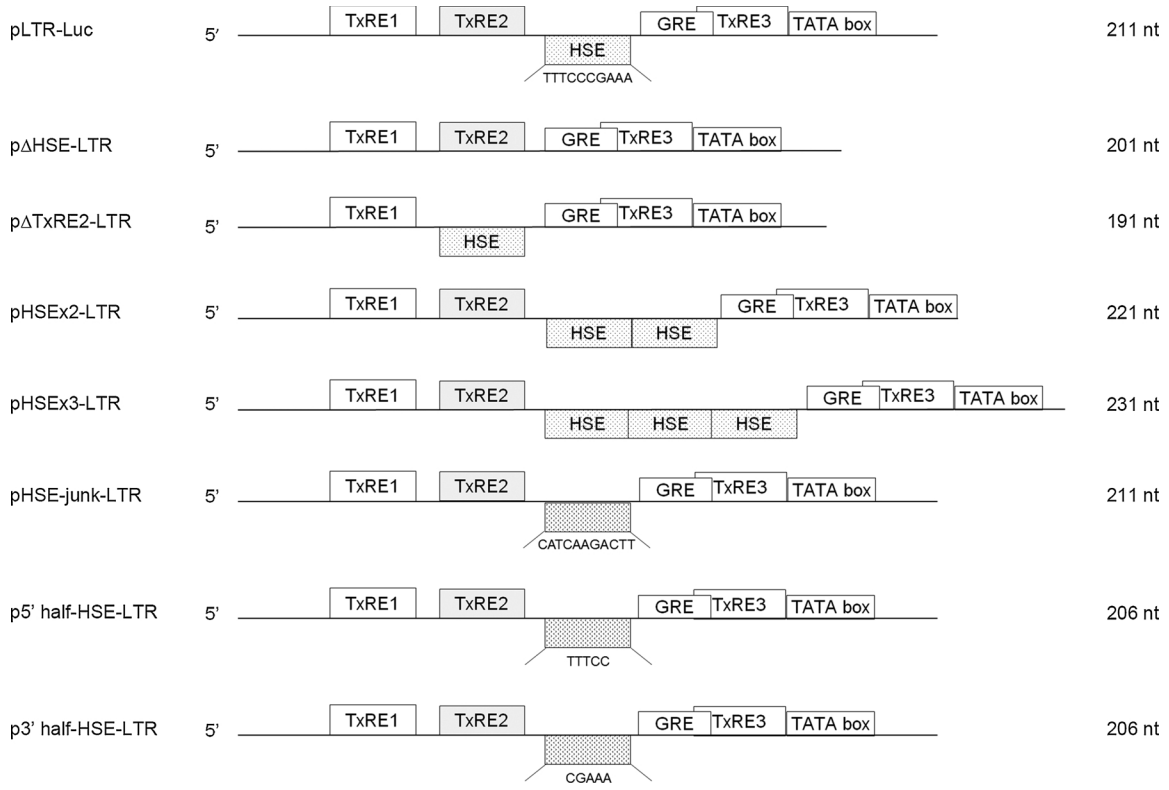

Fig. 1. Schematic representation of U3 region of LTR-luciferase reporter vectors that were used in this study. HSE: heat shock element (5′-TTTCCGAAA-3′), TxRE: Tax response element, GRE: glucocorticoid response element, TATA box: binding site of TATA-binding protein, nt: nucleotide.

0.83% NH_4Cl solution containing 0.01% EDTA, the leukocytes were separated by centrifugation and washed three times in phosphate-buffered saline. Eighteen tumor tissue samples from EBL cattle were confirmed to be infected with BLV by PCR, and used for the sequence analysis of LTR in proviral DNA. These samples were provided by a meat inspection center in Japan. DNA was extracted from the leukocytes (about 1×10^7 cells) and EBL tumor tissues (about 10 mg) using a DNeasy Blood & Tissue Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Total RNA was prepared using an RNeasy Mini Kit (QIAGEN), and complementary DNA (cDNA) was synthesized from 1 μg of RNA using a PrimeScript 1 st Strand cDNA Synthesis Kit (Takara Bio, Shiga, Japan).

2.2. Cell culture

The FLK-BLV cells were maintained in Eagle's minimal essential medium (E-MEM) containing 5% fetal calf serum (FCS), 100 U/ml penicillin, and 100 μg/ml streptomycin. CC81 cells that are a feline cell line with high susceptibility to BLV (Konishi et al., 2018) were maintained in E-MEM supplemented with 5% FCS, 0.3% tryptose phosphate broth, 100 U/ml penicillin, and 100 μg/ml streptomycin. These cells were cultured in a 37 °C incubator with 5% CO_2.

2.3. Sequence analysis of LTR in clinical samples

The LTR sequences in proviral DNA of EBL tumor tissues were amplified by semi-nested PCR using GoTaq Green Master Mix (Promega, Madison, WI). About 0.1 μg of DNA was used for PCR and the cycling conditions were as follows: 95 °C for 2 min; 35 cycles of denaturation at 95 °C for 30 s, annealing at 55 °C for 30 s, and extension at 72 °C for 35 s; and a final extension at 72 °C for 7 min. The primer sequences are detailed in Supplementary Table. The first-round PCR primers were LTR-1 F and LTR-559R, and the second-round PCR primers were LTR-1 F and LTR-531R. A 531-bp PCR product was expected. The PCR products were electrophoresed in a 2% agarose gel and stained with ethidium bromide. The amplicons were purified using a Wizard SV Gel and PCR Clean-Up System (Promega). The LTR sequences were analyzed using a BigDye Terminator v3.1 Cycle Sequencing Kit and an Applied Biosystems 3130 Genetic Analyzer (both Thermo Fisher Scientific, Waltham, MA). A multiple alignment was performed using the ClustalW program in GENETYX v13 software (GENETYX Corp, Tokyo, Japan).

2.4. Vector construction

2.4.1. LTR reporter vector

A 531-bp LTR sequence, which was composed of the U3, R, and U5 regions of BLV in fetal lamb kidney cells persistently infected with BLV (FLK-BLV) (EF600696) (Van der Maaten et al., 1972), was amplified using primers consisting of an LTR sequence with a *Xho*I or a *Hind*III site at the 5′ terminus, respectively (BLV-LTR-F-*Xho*I and BLV-LTR-R-*Hind*III, Supplementary Table). LTR amplification was performed using PrimeSTAR Max DNA Polymerase (Takara Bio) and primers at a concentration of 1 μM. PCR was performed over 35 cycles of 98 °C for 10 s, 55.6 °C for 15 s, and 72 °C for 5 s. The PCR product was purified using the Wizard SV Gel and PCR Clean-Up System (Promega). Adenylation of the blunt-end product was performed using LaboPass SP-Taq DNA polymerase (Hokkaido System Science, Hokkaido, Japan) at 72 °C for 30 min. Then, the product was cloned into a pCR2.1-TOPO vector using a TOPO TA Cloning Kit (Thermo Fisher Scientific) and amplified in One Shot TOP10 Chemically Competent *E. coli* (Thermo Fisher Scientific). The plasmid was harvested using a Wizard Plus SV Minipreps DNA Purification System (Promega). The LTR sequence was subcloned into a *Xho*I- and *Hind*III-digested pGL3 basic vector expressing firefly-luciferase (Promega) and was used as a pLTR-Luc vector.

Mutant vectors of pLTR-Luc were constructed using a PrimeSTAR Mutagenesis Basal Kit (Takara Bio) and primers shown in Supplementary table. An HSE sequence is composed of two or three

Table 1
SNPs found in BLV LTR sequences.

Sample No.	U3 (1-211)					R (212-440)	U5 (441-531)
	TxRE1 (48-69)	HSE (126-135)	GRE (139-151)	TATA box (169-175)	Other		
1	—	—	—	T175C	—	—	—
2	—	—	—	—	A117C	—	—
3	—	—	—	T175C	—	—	—
4	—	—	—	—	—	—	—
5	—	—	—	—	C27A	A315G	T448C
6	—	—	—	—	—	—	—
7	G66A	—	—	—	A117C	—	—
8	—	—	—	T175C	A208G	—	—
9	—	—	—	—	—	—	—
10	—	—	—	—	C113G	A424G	—
11	—	—	—	—	A117C	—	C486T
12	—	—	—	—	—	—	—
13	—	—	—	—	—	—	—
14	—	—	—	—	A117C	—	—
15	C66A	—	—	—	A117C	—	—
16	—	—	—	—	—	—	—
17	—	—	G148A	—	—	C245T	—
18	—	—	—	—	—	—	—

tandem repeats of a consensus motif (5′-nGAAn-3′). An HSE (5′-tTTCccGAAa-3′) was identified in the U3 region of pLTR-Luc and was deleted to obtain a pΔHSE-LTR vector. An additional one or two HSE tandem repeats were inserted into the 3′ end of the HSE in the pLTR-Luc to construct a pHSEx2-LTR or pHSEx3-LTR vector, respectively. A 5′ side motif 5′-tTTCc-3′ (5′-gGAAa-3′ in reverse orientation) and 3′ side 5′-gGAAa-3′ of the HSE in a pLTR-Luc were eliminated to construct a p3′half-HSE-LTR and p5′half-HSE-LTR vector, respectively. A pHSE-junk-LTR vector was constructed by replacing the HSE in a pLTR-Luc vector with a sequence of 5′-CATCAAGACTT-3′ that was identical to the HSE in its nucleotide composition and length but different in its sequence. The LTR of BLV contains three TxREs. The second TxRE (TxRE2) was eliminated from a pLTR-Luc to obtain a pΔTxRE2-LTR vector (Fig. 1).

2.4.2. *tax* expression vector

The *tax* gene of BLV was amplified from the FLK-BLV cell genome using PrimeSTAR Max DNA Polymerase and the primers shown in Supplementary Table. PCR was performed over 35 cycles of the following three steps: 98 °C for 10 s, 52 °C for 15 s, and 72 °C for 10 s. The PCR product was adenylated at the 3′ end, cloned into a pCR2.1-TOPO vector, and introduced into competent *E. coli* as described above. Then, the amplified plasmids were extracted using the Wizard Plus SV Minipreps DNA Purification System and were modified to insert a Kozak sequence (5′-GCCACC-3′) immediately upstream of the ATG start codon using a PrimeSTAR Mutagenesis Basal Kit (Takara Bio) according to the manufacturer's instructions. A FLAG sequence was appended to the 3′ end of the *tax* open reading frame (ORF) by PCR using the PrimeSTAR Max DNA Polymerase and a primer pair in which the reverse primer had a FLAG sequence at 3′ terminus. The *tax*-FLAG coding sequence was subcloned into a pIRESneo3 vector (Takara Bio) to obtain the Tax protein-expression vector (ptax).

2.4.3. *HSF* expression vector

The entire ORF of *HSF1* was amplified from the cDNA of blood collected from clinically asymptomatic cattle by reverse transcription (RT)-PCR using primers shown in Supplementary Table and cloned into a pCR2.1-TOPO vector. The harvested plasmids were digested with *Eco*RI and *Not*I and subcloned into a pIRESneo3 vector to construct the *HSF1* expression vector pHSF1. We also constructed a pHSF1-DBD deletion mutant of pLTR-Luc that expressed HSF1 lacking the DNA-binding domain. Primers for the deletion are shown in Supplementary Table.

2.5. Luciferase reporter assay

CC81 cells suspended at a concentration of 2×10^4 cells/0.1 ml were seeded in a 96-well plate and transfected with reporter plasmids at 100 ng/well and expression plasmids using the Lipofectamine LTX with Plus Reagent kit (Thermo Fisher Scientific). A pRL-TK vector (Promega) expressing *Renilla* luciferase was used as the internal control of transfection efficiency. The firefly and *Renilla* luciferase activities in each well were measured using a Dual-Luciferase Reporter Assay System (Promega) and a Centro LB960 microplate luminometer (Berthold Technologies, Bad Wildbad, Germany).

3. Results

3.1. HSE sequence in the BLV LTR U3 region

An HSE sequence (5′-tTTCccGAAa-3′) was identified in each of the 18 EBL samples. The HSE was located between the TxRE2 and GRE domains in the U3 region (Fig. 1). The HSE sequences in all samples did not have any mutations and were completely conserved. On the other hand, three kinds of single nucleotide polymorphisms (SNPs) were observed in other regulatory motifs. These LTR SNPs included nine patterns (Table 1). Two TxRE1 sequences in the 18 samples were found to have G66A or C66A nucleotide substitutions, and four TATA box sequences had T175C nucleotide substitutions.

3.2. LTR transcription activity by HSF1 expression

pHSF1 and pLTR-Luc vectors were co-introduced into CC81 cells. The HSF1 protein was detected 14 h after transfection, and its levels increased up to at least 21 h (Fig. 2A). The LTR-regulated luciferase activity was increased in cells with 100 ng/well of pHSF1 at 12 h without Tax protein expression and also in cells with 25 and 50 ng/well of pHSF1 after 24 h (Fig. 2B). When the Tax expression vector was transfected together with pHSF1 vector into cells, the LTR activity was 2.6-fold higher than that in cells with HSF-1 alone (Fig. 3). In contrast, the LTR activity was not increased by pHSF1-ΔDBD. Tax-induced LTR activation was suppressed by co-expression of HSF1-ΔDBD protein.

3.3. Requirements of the intact HSE sequence for the activation of LTR by HSF1

The U3 region of LTR has elements for the binding of host cell-derived transcription factors. When the HSE in the U3 region was eliminated from the pLTR-Luc vector, transactivation of the mutant LTR by HSF1 expression was reduced to approximately 1/10 of the intact LTR (Fig. 4A). Interestingly, Tax-driven LTR activity in cells that were transfected with the pΔHSE-LTR increased only up to half of that of the intact pLTR-Luc, although it was not statistically significant (Fig. 4B). Deletion of TxRE2 in three TxREs from the pLTR-Luc resulted in the significant attenuation of LTR activation by the transient Tax expression (Fig. 4B).

It was found that activation of the LTR by HSF1 was dependent on repeat number of HSEs in the LTR, whereas luciferase activities of pHSE-junk-LTR, p5′half-HSE-LTR, and p3′half-HSE-LTR vectors were comparable to that of pΔHSE-LTR (Fig. 5A). Regarding Tax expression, the LTR was activated in all reporter vectors except pΔTxRE2. However, Tax did not activate pHSEx2-LTR and pHSEx3-LTR vector (Fig. 5B).

4. Discussion

It has been clarified that BLV Tax protein activates proviral LTR to

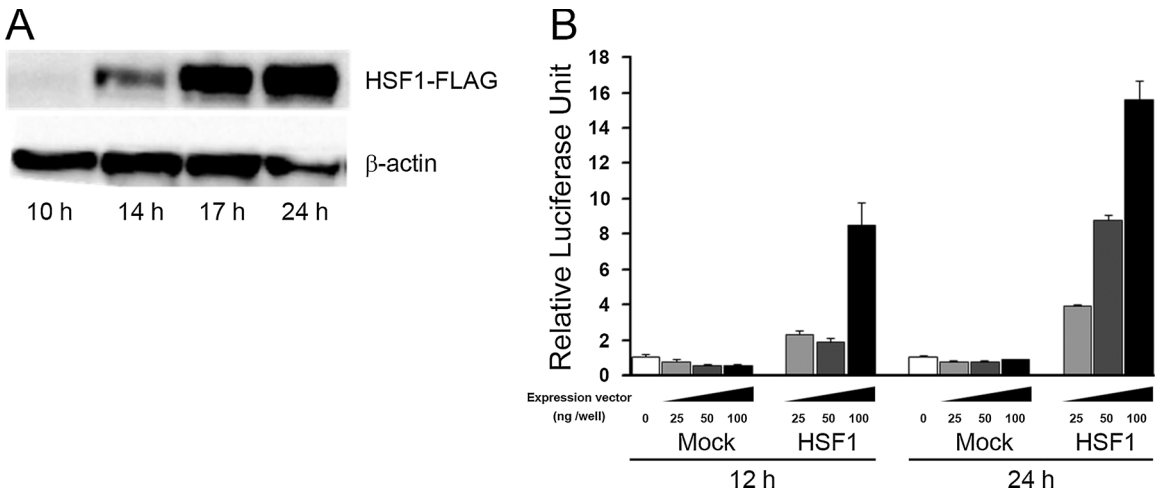

Fig. 2. HSF1 induces LTR activation in CC81 cells. (A) Upper: FLAG-tagged HSF1 protein expression in CC81 cells that were transfected with pHSF1 vector and analyzed by Western blot. Lower: β-actin as a loading control. (B) Luciferase activities of pLTR-Luc vector in CC81 cells that were co-transfected with or without pHSF1 vector.

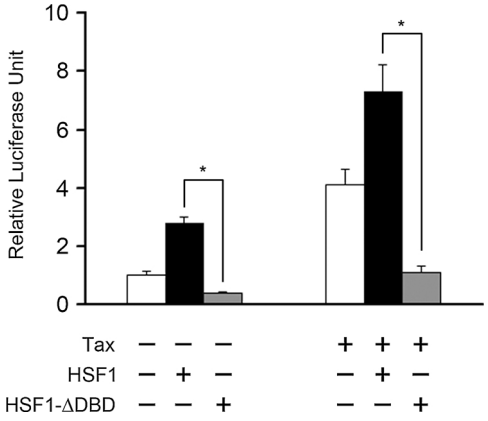

Fig. 3. DNA-binding domain of HSF1 protein is required to activate LTR by HSF1 and Tax protein expression. *$P < 0.05$ by Student's *t*-test.

induce viral gene expression and replication of the BLV genome. In a microarray analysis, the mutant Tax, which neither induced the viral particle production nor stimulated the transcriptional activity of BLV LTR, upregulated genes that were related to the stress responses (Arainga et al., 2012; Tajima and Aida, 2000). These findings indicate a novel function of the BLV Tax protein that stimulates the expression of host cell genes in addition to the LTR activation. On the other hand, the effects of host cell-derived factors on the LTR are unclear. Generally, HSP gene expression is regulated by HSFs that bind to the HSE in a target gene promoter (Amin et al., 1988; Sarge et al., 1993). It has been shown that HSP expression is involved in the protection against various infections (Haregewoin et al., 1989). Anti-HSP70 IgG in serum was shown to be higher in BLV-infected cattle than in uninfected cattle (Ungar-Waron et al., 1996). However, HSPs have been poorly investigated in relation to BLV proliferation. In the present study, it was first revealed that the LTR of BLV contained a functional HSE. The analyzed HSEs were identical in sequence in the 18 EBL cattle, suggesting that the HSE played an important role in the transactivation of LTR. This finding supports previous BLV LTR sequence analysis results (Pluta et al., 2018; Zhao et al., 2007). HSF1 activated LTR-driven transcription without Tax. Because the activation by HSF1 did not occur in LTRs that had a mutant HSE sequence, it was considered that the LTR activation by HSF1 protein depended on an intact HSE sequence. Additionally, HSF1 was found to enhance the LTR-transactivation ability of Tax protein. This data suggests that HSF1 and Tax can bind to an LTR sequence and exert an additive effect on the LTR activation.

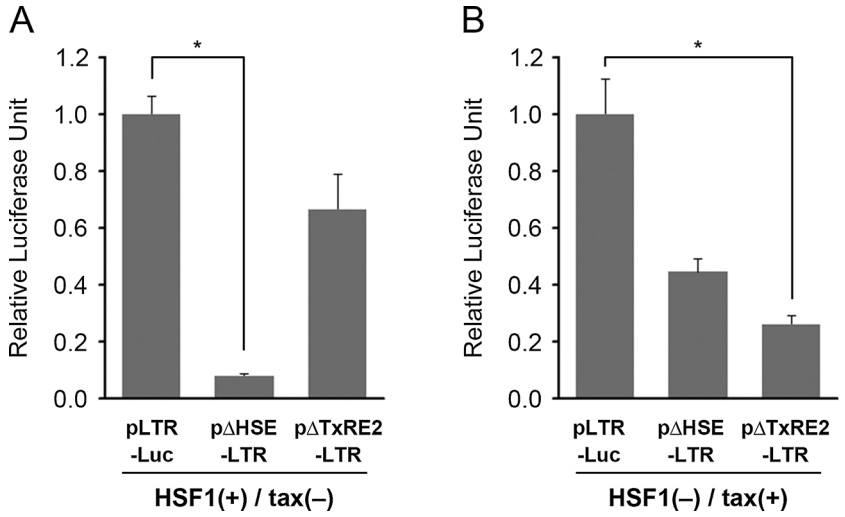

Fig. 4. HSE and TxRE in BLV LTR are necessary to activate LTR by HSF1 and Tax. Deletion of HSE (A) and TxRE2 (B) sequence in pLTR-Luc significantly inhibited upregulation of luciferase activity by HSF1 or Tax protein, respectively. *$P < 0.05$ by Student's *t*-test.

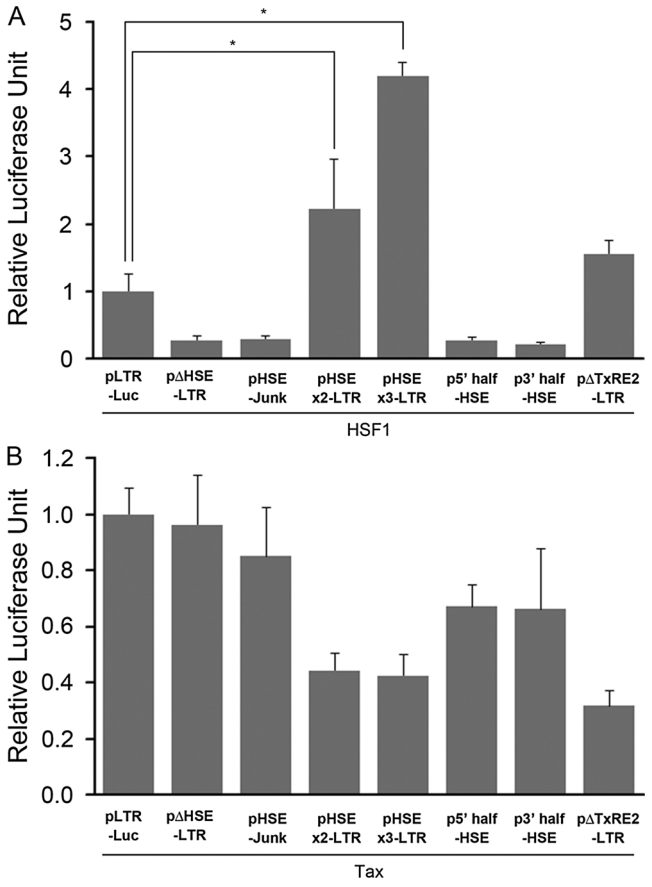

Fig. 5. Activation of LTR by HSF1 needs intact HSE. (A) Upregulation of luciferase activities were repeat number of HSE-dependent. (B) Increase of HSE-repeat number in LTR inhibit Tax-induced LTR activation.

The LTR of BLV has been shown to contain other *cis* elements that bind host-derived transcription factors. For example, BLV LTR has an NF-κB-like binding site and a PU-box, which is a promoter site of PU.1/Spi-B (Brooks et al., 1995; Dekoninck et al., 2003). The NF-κB in BLV LTR was stimulated by the expression of NF-κB protein (Brooks et al., 1998). PU.1- and Spi-B-binding elements have a purine-rich core motif (5´-GGAA-3´). A 2-bp mutation within this motif (5´-GGAA-3´ to 5´−CCAA-3´) abrogated PU.1/Spi-B binding and caused a marked decrease in LTR-driven basal gene expression (Dekoninck et al., 2003). The GGAA motif is contained in the HSE in LTR (3´- aAAGggCTTt -5´ in reverse orientation). The p5´half-HSE-LTR vector in the present study has a GGAA in the reverse strand of LTR, whereas the p3´half-HSE-LTR vector does not have the motif. Because luciferase activities between these two constructs were almost identical and, therefore, irrelevant to HSF1 or Tax expression, PU.1 and Spi-B were considered not to affect LTR activity in the present experiment.

HSF1 consists of an N-terminal DNA-binding domain, a coiled-coil oligomerization domain, a regulatory domain, and a transactivation domain (Wu, 1995). Monomeric HSF1 is stabilized by binding to molecular chaperones such as HSP70 and HSP90 (Abravaya et al., 1992; Nadeau et al., 1993; Neef et al., 2014; Zou et al., 1998). Under stress conditions, HSF1 may be displaced from its chaperone complexes by misfolded proteins, and DNA-binding activity is achieved through an intrinsic oligomerization tendency of HSF1 (Neudegger et al., 2016). In the present research, it was unexpected that the expression of a mutant HSF1, which lacked the DNA-binding domain, failed to activate LTR even in the presence of Tax protein. Although the precise mechanism was not elucidated, this suggests that a direct or indirect interaction with HSF1 was necessary for Tax protein to efficiently activate the LTR. On the other hand, contrary to our expectation, it was also demonstrated that LTR activation by Tax was impaired in mutant LTRs that contained two or three repeats of HSEs. These data suggest that the distance, molecular ratio, or order of TxRE and HSE in LTR are also important factors for the transactivation of BLV LTR.

Transactivator of transcription (Tat) and negative regulatory factor (Nef) are encoded in HIV-1 (Debaisieux et al., 2012; Simmons et al., 2001). HIV-1 Tat and Nef have been demonstrated to enhance viral replication and interact with cellular HSP40 and HSF1 (Glushakova et al., 1999; Joseph et al., 2003; Lundquist et al., 2004; Rawat and Mitra, 2011). HSF1 directly activates HIV-1-LTR promoter through binding to an HSF1-binding sequence on HIV-1 LTR and increases viral gene expression (Rawat and Mitra, 2011). In latent HIV-1, although there is Tat limitation, HSF1 also plays an essential role in reactivation (Pan et al., 2016). Although HSF1 has been poorly studied in human T-cell leukemia virus type 1 (HTLV-1), there is a concern that heat shock stress is one of the environmental factors that induces reactivation of the virus via enhanced Tax expression (Kunihiro et al., 2016). The stress response has been shown to increase the HTLV-1 LTR activity (Andrews et al., 1997), and HTLV-1 Tax has been associated with HSP90 and HSP70 (Cheng et al., 2001; Gao and Harhaj, 2013).

In conclusion, we found that an HSE consensus sequence is conserved among the LTR of BLV genomes. The HSE works as a promoter for transcription through the interaction of HSF1. Although the molecular mechanism is unelucidated, it is indicated that HSF1 activates LTR at the basal level without Tax. The sequence structure of LTR is suggested to be important for LTR transactivation.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.virusres.2019.197641.

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