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RNA polymerase III control elements are required for *trans*-activation by the murine retroviral long terminal repeat sequences

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ABSTRACT

RNA leukemia viruses induce T-cell lymphoblastic lymphomas or myeloid leukemias. Infection of cells with Moloney murine leukemia virus (M-MuLV) up-regulates the expression of a number of cellular genes, including those involved in T-lymphocyte activation. Previously, we demonstrated that this up-regulation occurs via the *trans*-activation activity of the M-MuLV long terminal repeat (LTR) sequences which produce an LTR-encoded transcript. Sequence analysis of the LTR revealed a potential transcription unit for RNA polymerase III (Pol III) within the U3 region that is actively occupied by Pol II factors. Here, we provide the direct evidence of involvement of Pol III in the *trans*-activation process and demonstrate the precise localization of the intragenic control elements for accurate and active Pol III transcription. Deletions of a copy of the directed repeats and further immediate upstream sequences significantly abrogated the generation of LTR-encoded transcript and abolished the *trans*-activational activity, whereas the deletion of a copy of directed repeats alone proportionally reduced the transcript size, but still retained moderately high *trans*-activational activity. In electrophoretic mobility shift assay, the fraction containing a multiple transcription factor TFIIIC complex strongly bound to the LTR-U3 probe containing the essential control elements. The specificity of the DNA-TFIIIC interaction was confirmed by conducting competition assays with DNA fragments containing a genuine Pol III-transcribed gene, VA1, and by vaccinia virus infection which stimulates the expression of Pol III factors. However, a deletion mutant lacking an essential control element bound to the TFIIIC complex poorly, consequently resulting in weak Pol III transcription as assessed by an IRES-GFP reporter system. This correlation strongly supports the possibility that the generation of LTR-encoded transcript is directed by Pol III. Therefore, this finding suggests the involvement of Pol III transcription in the retrovirus-induced activation of cellular genes, potentially contributing to leukemogenesis.

1. Introduction

A number of different types of recombinant retroviruses have been isolated from thymic neoplasms of mice. Moloney murine leukemia virus (M-MuLV) is a C-type non-acutely transforming retrovirus, which lacks oncogenes, but induces lymphoid neoplasia in mice after a long latent period through an indirect mechanism [1]. Recent studies have demonstrated that the genomic long terminal repeat (LTR) sequence determines the leukemogenicity and latency of M-MuLV-induced leukemia [2,3]. The LTR sequence of other MuLVs, including Friend-mink cell forming MuLV causing erythroid leukemia, is also known to determine the pathogenicity and tropism [4]. The LTR sequences contain enhancer elements, in addition to RNA polymerase II (Pol II) promoter elements, in the U3 region. It was previously reported that the M-MuLV LTR profoundly enhances the expression of cellular genes, including those encoding a number of proteins involved in T cell activation [5,6] and the *c-jun* proto-oncogene [7]. It is believed that the tandemly repeated sequences of the LTR are responsible for *trans*-activation, due to their ability to generate the LTR-encoded transcript.

Analysis of the short LTR sequences suggested the involvement of RNA polymerase III (Pol III) transcription in *trans*-activation. A major transcript is believed to be encoded by the putative intragenic promoter sequences of the U3 region. In general, Pol III-transcribed genes are characterized by an intragenic split promoter consisting of two major components, A and B Blocks [8]. Studies on Pol III transcription with relatively large deletions of the putative control elements proposed a set of potential intragenic control elements within the U3 region [9]. RT-PCR and *in vitro* transcription experiments in the presence of Pol II or III inhibitors indirectly supported

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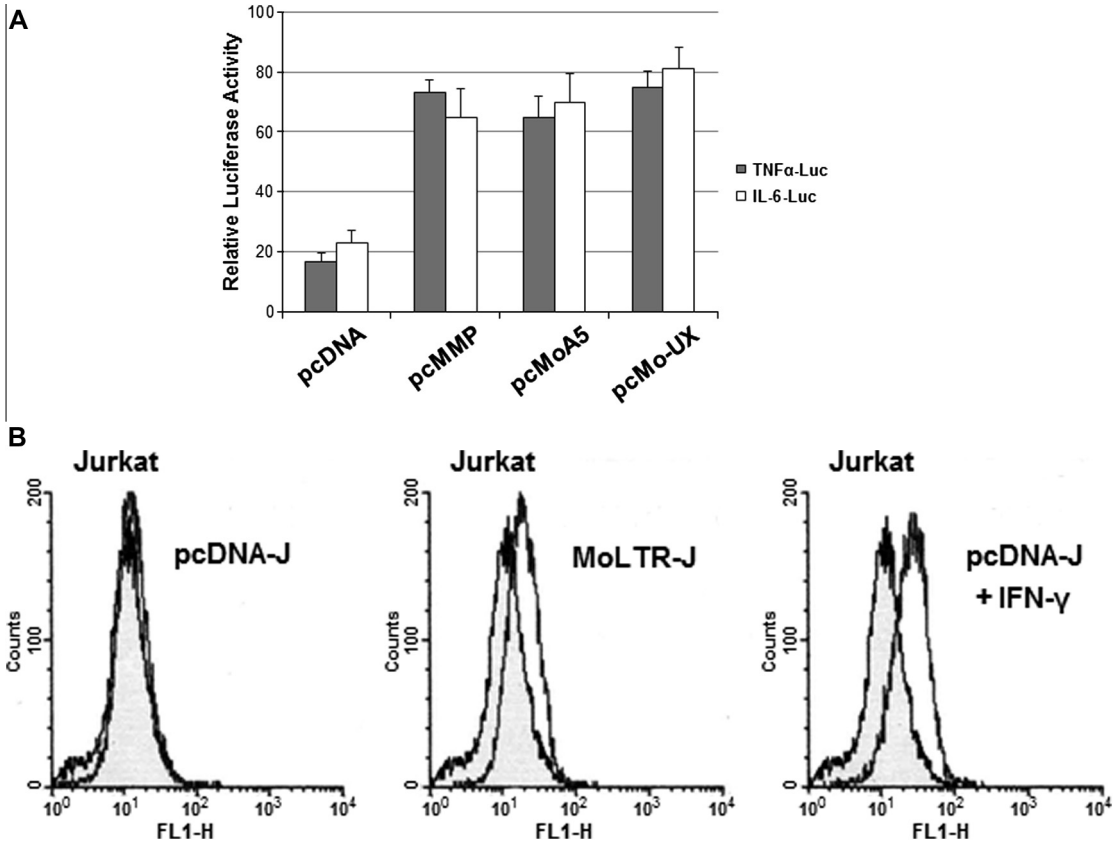

Fig. 1. *Trans*-activation of cellular genes by retroviral LTR sequences. (A) Jurkat cells were co-transfected with a reporter pTNFα-Luc or pIL6-Luc, and the indicated plasmids: pcDNA, pcMMP, pcMoA5, or pcMo-UX, and harvested after 24 h for luciferase assays. The data were expressed as means ± SD for at least three independent experiments. (B) FACS analysis of MHC class I antigen expression was carried out on pcDNA-J and MoLTR-J cells, which were Jurkat cells stably transfected with pcDNA or pcMoA5, respectively, and on Jurkat cells treated with recombinant human IFNγ (100 U/ml) for 48 h. Cells were stained with an antibody against native human MHC class I (W6/32).

the presence of the Pol III transcription unit in the U3 region. However, no direct experimental evidence was provided to ensure the putative Pol III transcription unit within the U3 region is functional in intact cells. In order to provide evidence for the existence of the active Pol III transcription unit and its correlation with functional activity, the localized intragenic control elements need to be identified more precisely, and their capability to interact with an essential Pol III factor, including the common factors TFIIIC and TFIIIB, in cells needs to be determined.

In this study, the functional role of a critical control element of the LTR U3 region in Pol III transcription and *trans*-activation was demonstrated. Direct evidence was provided to support the fact that the generation of the LTR-encoded transcript is closely correlated with the interaction with TFIIIC. This finding indicates an alternative mechanism of retrovirus-induced dysregulation of cellular genes.

2. Materials and methods

2.1. Plasmids

Plasmid pMoV9, a cloned provirus of M-MuLV, was used for LTR expression and construction of other retroviral vectors [10]. Plasmid pcMoA5 is a pMoV9 derivative containing a single 5′ LTR genomic sequence in pcDNA. The 3′ deletion mutant pcMo-UX was a pcMoA5 derivative with deletion downstream from the *XbaI* site. pcMo-UXdV is identical to pcMo-UX except for a deletion of *EcoRV-EcoRV* in the U3 region. pcMo-UXPdV was the same construct as pcMo-UXdV, but with total deletion of 86 bp upstream from the 5′ end of the *EcoRV* site using a recombinant circle PCR mutagenesis reaction. A retroviral transfer vector pcMMP containing both the 5′ and 3′ LTRs of the provirus was provided by Dr. R.C. Mulligan. A reporter plasmid, pTNFα-Luc, containing TNFα gene promoter (−1274) driving the luciferase gene, was a gift from Dr. B.P. Giroir. Plasmids pG2A-MoUX and pG2A-MoUXPdV were constructed by inserting the LTR portion of pcMo-UX and pcMo-UXdV into the pGEM2 vector, respectively. Plasmids pG2A-MoUX-IRES-GFP and pG2A-MoUXPdV-IRES-GFP were constructed by inserting a 1372 bp fragment of the enhanced GFP-encoding region under the control of the internal ribosome entry site (IRES) into the *XbaI* sites of the pG2A-MoUX and pG2A-MoUXPdV, respectively.

2.2. Cell culture and virus infection

Balb/c 3T3, human osteosarcoma 143B and human T lymphoblastoid Jurkat cell lines were obtained from the American Type Culture Collection (Rockville, M.D., USA) and maintained as recommended. Transfection was conducted using Effectene reagent (Qiagen). Co-transfection with the pRSV-β-galactosidase plasmid and normalization of β-galactosidase activity were carried out to assess transfection efficiency. Long-term cell lines pcDNA-J and MoLTR-J were generated by co-transfection of Jurkat cells with the selection marker pSV2neo and pcDNA or pcMo-UX, respectively, and subsequently selected in G418-containing medium.

Recombinant vaccinia virus harboring the T7 polymerase gene (vTF7-3) was a kind gift of Drs. T. Fuerst and B. Moss (Division of AIDS, NIAID, NIH, USA). A monolayer of 143B cells was treated with VTF7 at a multiplicity of infection of 2 to ensure infection of >95% of the cells [11].

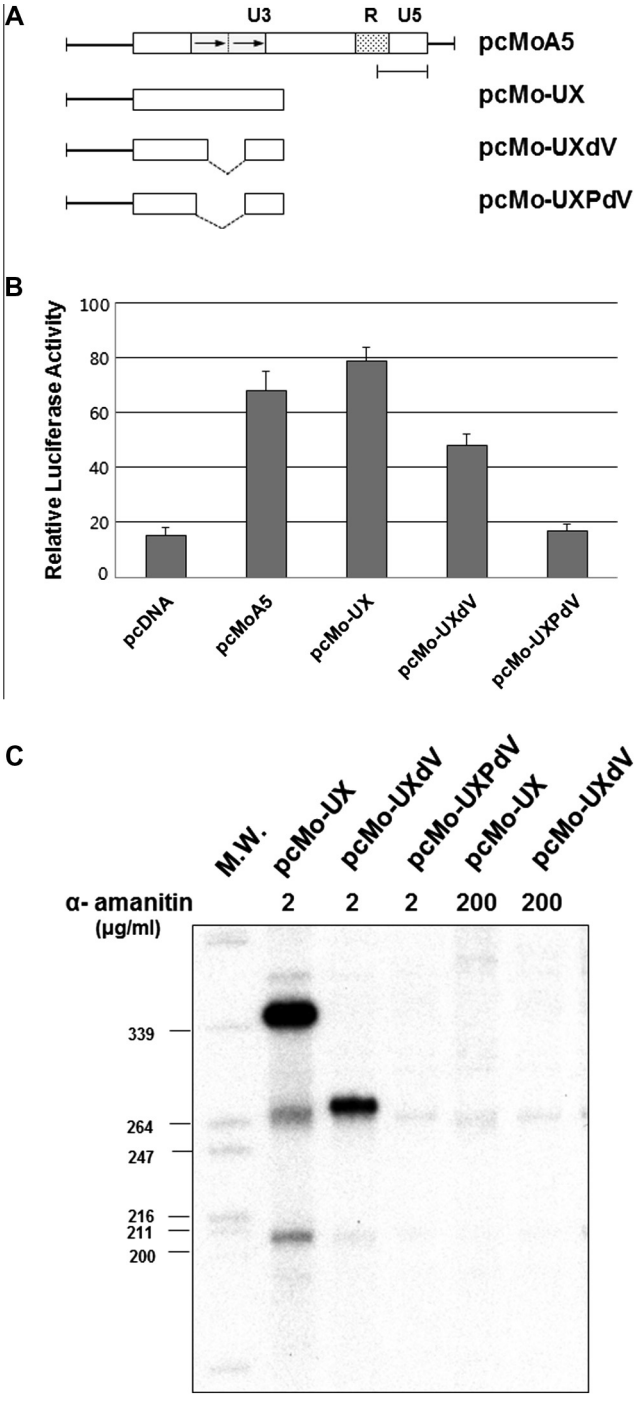

Fig. 2. Localization of internal control unit for LTR-encoded transcript generation and *trans*-activation. (A) The diagram shows the genomic structure of pcMoA5 and its derivatives, which were constructed for localization of the control unit. The open bar represents the portions of M-MMLV LTR that were included in each plasmid construct. The positions of direct repeats within the U3 are indicated by arrows. Scale bar, 100 bp. (B) Balb/c cells were transiently co-transfected with a reporter, pTNFα-Luc, and the indicated plasmids. Data are means ± SD of at least three separate experiments. (C) *In vitro* transcription analysis of LTR mutants. The indicated LTR constructs were used as templates for *in vitro* transcription with S100 extracts from Jurkat cells, as described in Section 2. Reactions were performed in the presence of 2 or 200 μg/ml of α-amanitin with the indicated constructs. Lamda DNA fragments digested with *PstI* were used as the M.W. size marker.

2.3. Fractionation of nuclear extracts

Nuclear extracts were prepared from HeLa cells using the procedure of Dignam et al. [12], except that the attached cells were used. Nuclear extracts in buffer A (20 mM HEPES (pH 7.9), 20% (V/V) glycerol, 0.2 mM EDTA, 0.5 mM PMSF) containing 0.1 M KCl was applied to a phosphocellulose column equilibrated with the same buffer. The column was washed with buffer A and then the bound proteins were sequentially step-eluted with buffer A containing 0.1, 0.35, 0.6, or 1.0 M KCl [13]. The flow-through and step-eluted fractions were pooled on the basis of protein concentration, as determined by Bradford assay. These fractions were concentrated by a 30 K NMWL (nominal molecular weight limit) Centricon filter (Millipore, USA) for EMSA.

2.4. Electrophoretic mobility shift assay (EM)

The final concentrations of the binding reactions were 10 mM HEPES-NaOH (pH 7.8), 50 mM potassium glutamate, 0.1 M KCl, 5 mM $MgCl_2$, 1 mM DTT, 5% glycerol, 0.5–1.5 μg of poly (dI:dC) (Sigma) and 4 μg of the concentrated protein. In EMSA, the 129 bp (*XbaI-BstEII*) from pMT2VA, 202 bp (*Sau3AI-XbaI*) from pcMoA5, 127 bp (*Sau3AI-XbaI*) fom pcMo-UXdV, and 116 bp (*Sau3AI-XbaI*) from pcMo-UXPdV fragments were end-labeled with [α-^{32}P]dCTP and used for binding reaction as described previously [7]. 143B cells were infected with vaccinia virus (VTF7-3) as previously described with minor modifications [14]. Antibody against TFIIIC220 was generously provided by Dr. A. J. Berk.

2.5. Preparation of Jurkat cell extracts and in vitro transcription

Jurkat cell extracts for *in vitro* transcription were prepared as previously described with minor modifications [15]. The reactions were directly processed for electrophoresis when RNA was labeled *in vitro*. For the synthesis of α-^{32}P-RNA, 25 μCi of [α-^{32}P] GTP (3000 Ci/mmol), 25 μM unlabeled GTP, and 400 μM ATP, CTP, and UTP were used.

2.6. Fluorescence-activated cell sorter

Immunofluorescence analysis of the endogenous MHC class I antigen expressed by cells was performed as described elsewhere [6]. Live cells were stained with monoclonal antibody W6/32, followed by fluorescein-conjugated, affinity-purified goat anti-mouse antibody to the Fab fragment, and analyzed on a FACScan fluorescence-activated cell sorter. Primary antibody W6/32 was prepared from hybridoma cell lines producing a monoclonal antibody specific for human MHC class I antigen.

3. Results and discussion

3.1. trans-Activation of cellular genes by retroviral LTR sequences

We previously demonstrated that the M-MuLV long terminal repeat (LTR) *up*-regulates specific cellular genes. M-MuLV *trans*-activates a number of genes, including T cell surface proteins [5,6] as well as AP-1 transcription factor [7]. These increases of the transcripts of specific cellular genes are attributed to the *trans*-activation activity of LTR-encoded transcripts. The portion of M-MuLV LTR capable of *trans*-activation was mapped to the U3 region [9]. In order to eliminate the possibility that the *trans*-activation by the LTR U3 region results from the background activity of different backbone plasmids, the LTR-containing sequences were subcloned in the same backbone plasmid, pcDNA3.1(+), that was used for pcMMP construct containing both the 5′ and 3′ LTRs. The constructs pcMoA5 and pcMo-UX contained the entire 5′ LTR and its U3 enhancer region, respectively. These plasmids were co-transfected into Jurkat cells with pTNFα-Luc or pIL6-Luc (Fig. 1A). All retroviral vectors used in this experiment similarly

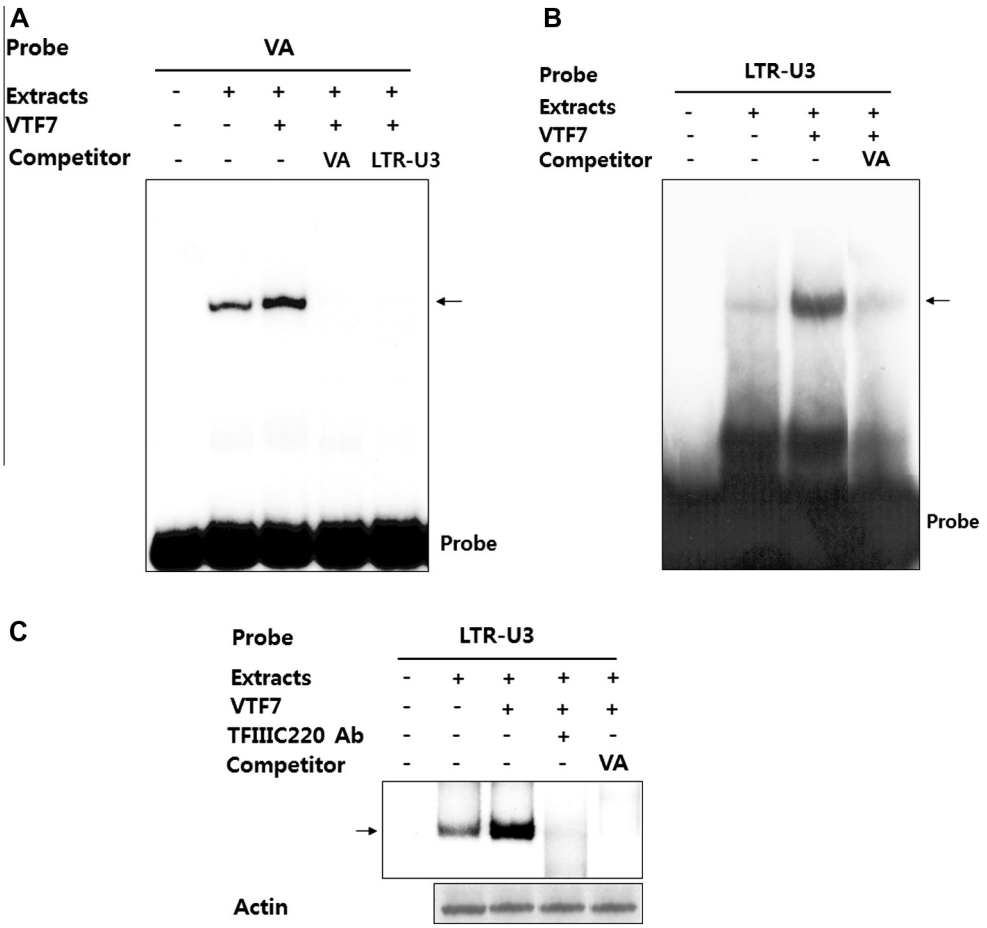

Fig. 3. Specific binding of TFIIIC complex with Pol III internal control elements. EMSAs were performed with either VA1 gene probe (−30 to +99) (A) or LTR-U3 (*Sau3AI-XbaI* from pcMoA5) probe (B and C), as indicated. Extracts of 143B cells with (+) or without (−) vaccinia virus infection (VTF7) were prepared. 100-fold molar excess of unlabeled VA1 gene (A, B and C) or LTR-U3 fragments (A) was used for specific competition assays. Supershift assays were performed with antibody against TFCIII220 (C). The arrow indicates the band specific for TFIIIC binding.

increased the expression levels of the cytokine reporter genes, as compared to cells transfected with the plasmid backbone pcDNA without the LTR. These results confirm that the sequences containing a subgenomic portion of the U3 region are capable of *trans*-activation of the reporter genes. Therefore, the cytokine genes, TNFα and IL-6, can belong to the group of genes activated by the M-MuLV LTR. Cytokines are well known to be important constituents of immune cell activation, acting as physiological inductive signals in the regulation of immune responses against foreign organisms, such as viruses and bacteria. Among them, TNFα and IL-6 are major components in the LPS-induced cytokine cascade in innate immune response. TNFα also can stimulate both pro- and anti-apoptotic signals in tumor cells, endothelial cells, macrophages and most other cells within the tumor microenvironment [16]. In combination with TNFα, IL-6 stimulates the expansion and cytotoxicity of naive $CD8^+$ T cells *in vitro* [17]. However, the precise roles of these two cytokines played in retroviral gene-induced leukemogenesis remain to be determined.

Whether a single 5′ LTR sequence could activate the MHC class I gene was also investigated. In this work, to eliminate the possibility that activation of the responsive genes by co-transfection of the LTR was due to inappropriate artifacts such as a physical linkage between co-transfected DNA, the long-term cell line MoLTR-J with a single 5′ LTR was employed, and monitoring of the endogenous MHC class I antigen was constructed. The level of MHC antigen expression was increased by 2-fold in the cells stably transfected with the 5′ LTR (MoLTR-J), and by 3-fold in the presence of IFNγ as a positive control (Fig. 1B), implying the independence of the location of the LTR *trans*-activator or responsive cellular genes. These results indicate that the LTR U3 sequence activates a set of important constituents involved in immune cell activation upon viral infection.

3.2. Localization of internal control unit for LTR-encoded transcript generation and trans-activation

It was demonstrated that cells transfected with a vector containing about 300 bp of the U3 sequences (pcMo-UX) had increased expression of specific cellular genes. The strong *trans*-activational activity of the short U3 sequences, which did not contain the minimal Pol II promoter, implied that these phenomena should be independent of Pol II. Analysis of the U3 enhancer region of the LTR and its flanking sequences suggests the presence of potential internal control elements for Pol III transcription. As shown in Fig. 2A and B, pcMo-UX expression resulted in a high *trans*-activation in this assay. In order to investigate the precise intragenic control region required for Pol III, deletions were made within the U3 region. An internal deletion of a copy of 75 bp directed repeats (pcMo-UXdV) still had moderately high *trans*-activational activity, but with reduced activity as compared to pcMo-UX. It is therefore likely that the direct repeat sequence contributes to the activation of the TNFα gene. However, further deletion of 11 bp upstream from the directed repeat (pcMo-UXPdV), which may include a putative consensus sequence for Pol III

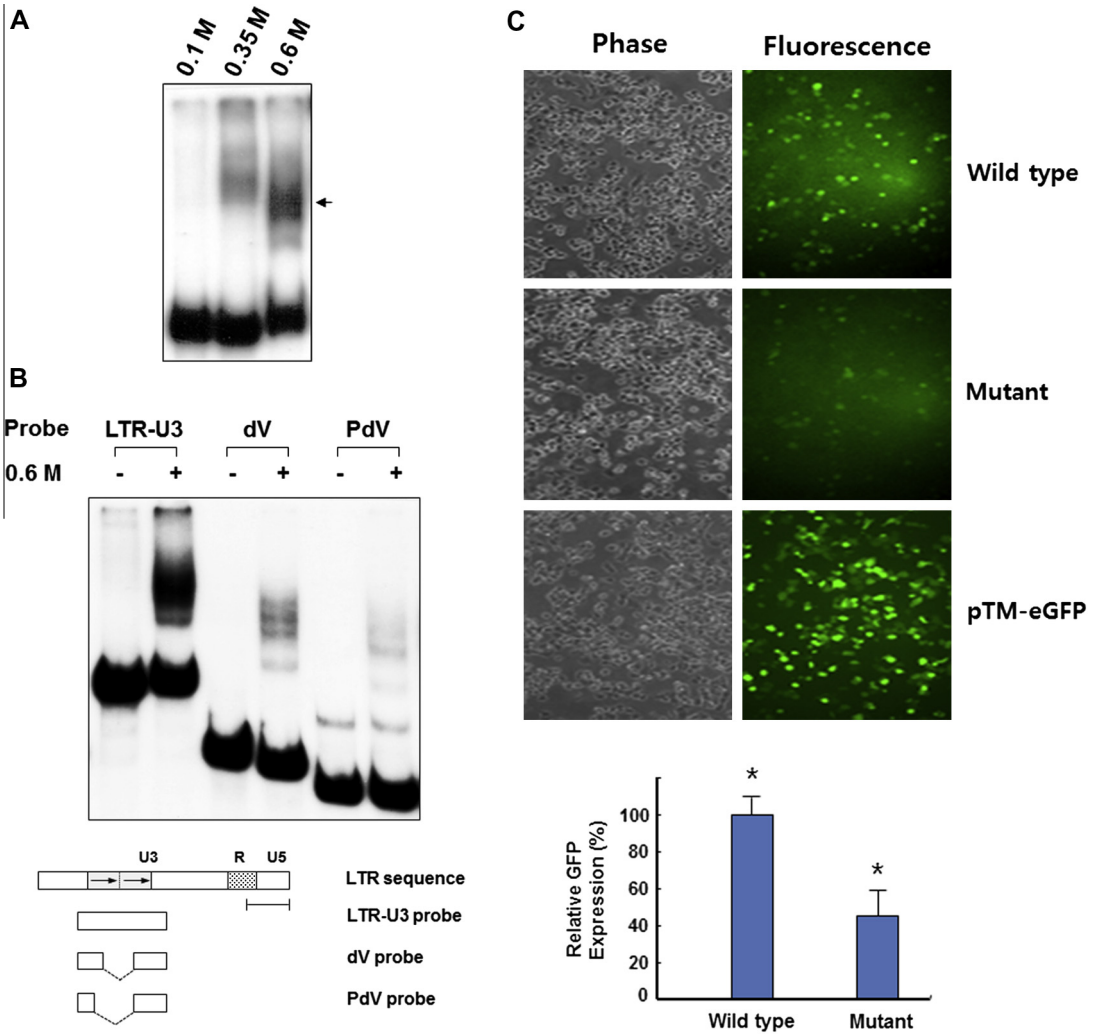

Fig. 4. Binding activity of LTR with TFIIIC is correlated with generation of the LTR-encoded transcript. (A) EMSA was performed with a 129 bp end-labeled VA probe and the indicated fractionations eluted with 0–0.1 (0.1 M), 0.1–0.35 (0.35 M), and 0.35–0.6 M KCl (0.6 M) buffer, which contained TFIIIA, TFIIIB, and TFIIIC from HeLa cells, respectively. (B) EMSA was performed in the presence (+) or absence (−) of the TFIIIC fraction (0.6 M) with the indicated radiolabeled probes: LTR-U3 probe, *Sau3AI-XbaI* gene fragment from pcMo-UX; dV probe, *Sau3AI-XbaI* gene fragment of pcMo-UXdV; PdV probe, *Sau3AI-XbaI* gene fragment of pcMo-UXPdV. The schematic diagrams depict the various probes derived from LTR-U3 fragments. The positions of direct repeats are indicated by the arrows. Scale bar, 100 bp. (C) GFP expression driven by the LTR-IRES system. After transfection with the indicated vector into 143B cells that were infected with VTF7, the GFP expression was analyzed with fluorescence microscopy. Plasmids pG2A-MoUX-IRES-GFP (Wild type) and pG2A-MoUXPdV-IRES-GFP (Mutant) contain the LTR portion of pcMo-UX and pcMo-UXPdV, respectively. pTM-eGFP was used as a positive control for TF7 expression. Bar graphs are the means ± SD for at least three independent experiments. Statistical significance was relative to the mock, and was determined using the *t*-test (*$p < 0.01$).

transcription, significantly reduced the *trans*-activational activity. The above data demonstrated that the deleted sequence included a key element, such as an A Block, for Pol III transcription. However, it is also possible that the deleted sequence is a part of an additionally required Pol III promoter element rather than a fixed A Block, as tRNA- or 5S-type polymerase III promoter elements have been described to require an external upstream region for accurate initiation of transcription [18].

As shown in Fig. 2C, a major LTR-derived RNA transcript was produced from pcMo-UX and pcMo-UXdV in the presence of 2 μg/ml of α-amanitin, a Pol II inhibitor. However, the transcription was inhibited with a higher concentration of α-amanitin (200 μg/ml), which should abrogate the normal Pol III activity. The deletion of a copy of the direct repeat sequence (75 bp) reduced both the size and level of the transcripts. As expected, the transcript of 270 nucleotides (nt) generated from pcMo-UXdV was 75 nt shorter than the major transcript from pcMo-UX (345 nt). All major transcripts appeared to be Pol III transcripts, as judged by the effects of α-amanitin. However, pcMo-UXPdV generated faint levels of transcripts. The Pol III transcription of pcMo-UXPdV was more efficiently blocked compared to the previous deletion mutant pGUXDP [9] (data not shown). These results indicate that the ability of mutant LTRs to generate transcripts correlates with their *trans*-activation activity, and that a potential internal control region for Pol III is located around the directed repeat sequence.

3.3. Specific binding of TFIIIC complex with Pol III internal control elements

In many types of Pol III-dependent genes, tRNAs and VA1 genes especially require TFIIIC binding to their transcription control elements [19]. In order to assess the contribution of TFIIIC to the generation of LTR-encoded transcripts, EMSAs were carried out. For identification of the specific binding complex, the vaccinia virus (VTF7) infection system, which activates Pol III transcription machinery [11], was applied herein. It can be seen in Fig. 3A and B that the DNA binding activity to either VA or LTR-U3 probe was greatly augmented when the nuclear extracts from VTF7-infected

cells were utilized. However, a 100-fold excess of either unlabeled VA or LTR-U3 probe efficiently competed for binding activity, indicating that the DNA binding activity of the probes was specific, and that the portion of the LTR-U3 probe contains a Pol III consensus, which binds strongly to the Pol III transcription factor TFIIIC. The specific binding of TFIIIC was ascertained by an antibody against TFIIIC220, as shown in Fig. 3C. These results strongly suggest the involvement of Pol III in the generation of LTR-encoded transcript.

3.4. Binding activity of LTR with TFIIIC is correlated with the generation of LTR-encoded transcript

Next, whether TFIIIC binding is indeed correlated with transcript generation and the *trans*-activation activity was examined. In order to assess the contribution of TFIIIC to LTR U3-driven transcription, TFIII factors were partially purified through phosphocellulose chromatography. Fractionation was carried out by sequential step-elution with buffers containing 0–0.1, 0.1–0.35, and 0.35–0.6 M KCl, mainly recovering TFIIIA, TFIIIB, and TFIIIC, respectively [13]. TFIIIC in the 0.35–0.6 M KCl nuclear protein fraction (0.6 M fraction) strongly bound to the VA probe in EMSA, as shown in Fig. 4A. Using the 0.6 M fraction, this experiment was extended to test whether TFIIIC factor binding to LTR probes was correlated with the LTR U3-driven transcription and the observed *trans*-activation activity. In Fig. 4B, discretely retarded bands were observed in the 0.6 M fraction, but the band intensities of each probe were closely related with their *trans*-activational activity. Although the dV probe contained the same sequence as the LTR-U3, excluding a copy of the directed repeat, absence of the directed repeat sequence may not be sufficient to allow efficient binding of TFIIIC in terms of the DNA context, which may result in weaker transcription and *trans*-activation. In case of the PdV probe, which lacked only 11 bp in addition to the copy of the directed repeat sequence, the binding activity was greatly reduced, suggesting that TFIIIC bound to the PdV probe very poorly because the additional deletion of 11 bp, as a putative control element, was critical for Pol III transcription. To support the significance of the control elements in LTR-encoded transcript generation in intact cells, a reporter of GFP expression driven by LTR-IRES were constructed. As shown in Fig. 4C, the GFP expression driven by the mutant LTR-IRES of pG2A-MoUXPdV-IRES-GFP was found to be lower than that of pG2A-MoUX-IRES-GFP. Although a bigger difference in RNA production between the LTR mutants was observed in the *in vitro* assays, which utilized a high concentration of RNase inhibitors, the GFP expression data in intact cells were generally consistent with the pattern of previous data.

In conclusion, this study provided critical evidences that the LTR-encoded transcript is a product of Pol III, and that both level and length of the transcript encoded in the U3 region affect the *trans*-activation activity. It is plausible that the 11 bp includes a control element of the Pol III promoter, GGCCAAACAGG, which is homologous with the A Block consensus sequence, RRYNNARY-GG, of tRNA and human Alu-family genes [20]. It is interesting to consider that the U3 region of the LTR identified herein has been reported as a determinant of the leukemogenicity of murine leukemia viruses. Therefore, it is important to investigate the mechanism of Pol III transcription further to determine how it is controlled in retrovirus-infected mammalian cells in coordination with cell growth and replication.

Acknowledgments

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