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# Activation of Caprine Arthritis-Encephalitis Virus Long Terminal Repeat by Gamma Interferon

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**Caprine arthritis-encephalitis virus (CAEV) is a lymphotropic lentivirus whose replication increases during monocyte maturation. We examined gene expression directed by the CAEV long terminal repeat (LTR) in a promonocytic cell line stimulated with several agents. Our results demonstrate that the CAEV LTR is activated by treatment of immature monocytes with gamma interferon (IFN-γ) or a phorbol ester but not with tumor necrosis factor alpha or lipopolysaccharide. The *cis*-acting element in the LTR for the IFN-γ response localizes to a duplicated 70-bp motif that contains an IFN-γ response element, the gamma-activated site. One copy of the motif is necessary and sufficient for the response to IFN-γ. Multiple copies contribute to basal transcriptional activity in the context of a heterologous promoter. This IFN-γ response element in the CAEV LTR differs from the element required for the response to phorbol esters. Thus, activation of the CAEV LTR in monocytes that are stimulated by IFN-γ, a cytokine that is secreted in response to viral infections, could contribute to conversion from latent to high-level viral replication in infected hosts.**

Caprine arthritis-encephalitis virus (CAEV) is a lentivirus that causes a symmetric, peripheral arthritis in adult goats that have been infected since birth (4, 14). Members of the lentivirus family include human immunodeficiency virus (HIV), ovine visna virus, and equine infectious anemia virus (EIAV) (10). Like infections with other members of the lentivirus family, infection with CAEV is characterized by prolonged periods of latency, an absence of oncogenic transformation in host cells, and tropism for mononuclear cells (10). During initial infection of monocyte precursors, viral replication is restricted. Differentiation of infected monocytes into macrophages results in increased viral expression and an associated inflammatory response (19, 21). Development of clinical manifestations localizes to tissues in which infected macrophages express CAEV (15). Thus, regulation of CAEV expression during monocyte differentiation is an essential step during disease pathogenesis.

Several signaling pathways have been shown to be important in regulation of lentiviruses during monocyte differentiation. Stimulation through these pathways can induce transcriptional factors that recognize sites in viral long terminal repeats (LTRs). The essential second messenger for regulation of the HIV type 1 (HIV-1) LTR in monocytes is nuclear factor κB (NF-κB) (9). Increased expression of the HIV-2 LTR during monocyte differentiation is dependent on binding sites for NF-κB and for members of the *ets* family of proto-oncogenes (13). The transcriptional factor required for visna virus LTR activation is the FOS-JUN heterodimer (25). Thus, several cellular transcriptional factors have been found to be involved in regulation of lentiviruses during monocyte differentiation.

Another second-messenger pathway in monocytes is stimulated by gamma interferon (IFN-γ), a cytokine secreted by activated T cells and natural killer cells in response to viral infections (5). Perturbation of IFN-γ receptors leads to tyrosine phosphorylation of members of the Janus kinase family (Jak1 and Jak2), tyrosine phosphorylation of STAT1α (signal transducer and activator of transcription), and new expression of several cellular genes (5, 6). Regulation of a lentivirus by this essential signaling pathway in monocytes has not yet been described.

Because regulation of CAEV expression increases during monocyte differentiation, we hypothesized that the CAEV LTR could be transcriptionally activated by signaling pathways in monocytes. We examined CAEV LTR-directed gene expression in the promonocytic cell line U937 (27). We demonstrate that the CAEV LTR is activated by IFN-γ signaling pathways in this promonocytic cell line and localize a *cis*-acting element required for the response. This is the first demonstration of regulation of a lentivirus by stimulation of monocytes with IFN-γ.

To investigate regulation of the CAEV LTR by different signaling pathways activated during monocyte differentiation, we performed transient transfections in U937, a human promonocyte cell line (27). U937 cells were transfected with a plasmid containing the CAEV LTR (Co isolate) upstream from the bacterial chloramphenicol acetyltransferase (CAT) reporter gene, called pCAEV-LTR-CAT (12) (kind gift of J. Clements). Transient transfections of U937 cells were performed with DEAE-dextran by using previously published methods (23). Twenty-four hours after transfection, U937 cells were stimulated with agents that activate signaling pathways induced during differentiation of this cell line into a mature phenotype: IFN-γ, phorbol myristate acetate (PMA), tumor necrosis factor alpha (TNF-α), and lipopolysaccharide (LPS) (18, 22). CAEV LTR-directed gene expression was activated 8.7-fold by treatment with IFN-γ and 5.1-fold by treatment with PMA (Fig. 1). TNF-α and LPS did not affect expression of pCAEV-LTR-CAT in U937 cells. Thus, CAEV LTR-directed gene expression is activated by signaling pathways induced by IFN-γ and by PMA in this promonocytic cell line.

To demonstrate that the stimulatory agents were effective, we examined expression of major histocompatibility complex (MHC) class II molecules, which are encoded by cellular genes activated by some of these agents (8, 11). We assessed the surface expression of these molecules by indirect immunofluorescence (26) after stimulation with IFN-γ, PMA, and

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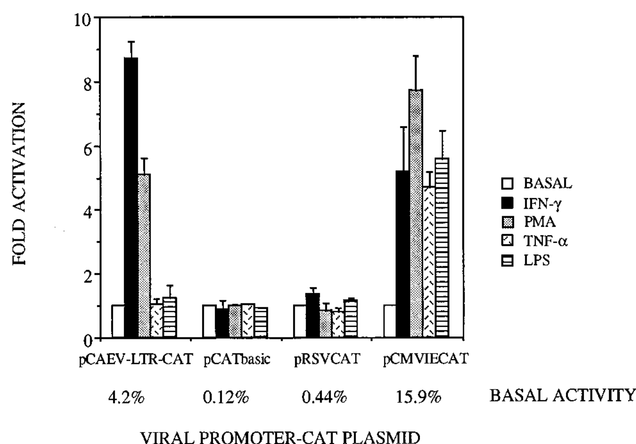


FIG. 1. Regulation of the CAEV LTR by monocyte differentiation. U937 cells were transiently transfected by the DEAE-dextran method (23) with the indicated plasmids that contained viral promoters upstream from the CAT reporter gene. Transfected cells were stimulated with medium alone (basal), IFN-γ (200 U/ml), PMA (50 ng/ml), TNF-α (500 U/ml), or LPS (1 μg/ml) for 24 h prior to harvesting. Fold activation was calculated as the ratio of CAT activity from stimulated cells over CAT activity from unstimulated cells. Data are the averages ± standard errors of the means from at least three independent transfections.

TNF-α. In agreement with published observations, increased surface expression of MHC class II molecules demonstrates that these agents adequately stimulated signaling pathways that lead to differentiation of this promonocytic cell line (Fig. 2) (8).

As a positive control to demonstrate that each stimulatory agent activated a promoter that responds to monocyte differentiation, we examined gene expression directed by the cytomegalovirus immediate-early promoter upstream from the CAT reporter gene in pCMVIECAT (3) (kind gift of P. Barry). Treatment of U937 cells transiently transfected with pCMVIECAT resulted in activation of this promoter with IFN-γ, PMA, TNF-α, and LPS, which is consistent with the observation that differentiated monocytes support productive cytomegalovirus infection (Fig. 1) (16).

To demonstrate specificity of stimulation of the CAEV LTR by IFN-γ and PMA, we examined effects of these agents on another retroviral LTR, the Rous sarcoma virus LTR, and on a promoterless CAT gene. IFN-γ, PMA, TNF-α, and LPS did not activate expression directed by the Rous sarcoma virus LTR upstream from the CAT reporter gene (pRSVCAT [28]) or expression of the CAT gene in the absence of any promoter in pCATbasic (Promega) (Fig. 1).

To determine optimal conditions for activation of the CAEV LTR by IFN-γ, a time course and dose response curve were performed in transiently transfected U937 cells. Stimulation of U937 cells for 4 to 48 h prior to harvesting demonstrated a small increase in expression at 4 h and maximal activation at 32 h (Fig. 3A). These kinetics are consistent with biphasic effects of IFN-γ. IFN-γ causes at short times (2 to 4 h) immediate transcriptional activation of one set of cellular genes and delayed transcription of another set of cellular genes that require new protein synthesis (6).

The dose-response curve of activation of the CAEV LTR showed the maximal response at greater than 10 U of IFN-γ per ml (Fig. 3B). Activation of the CAEV LTR was observed with as little as 1 U of IFN-γ per ml. To compare the dose response of CAEV LTR activation with the expression of cellular markers of differentiation, we monitored the surface expression of immunoglobulin receptor FcγRI (CD64) as well as MHC class II molecules by flow cytometry. Results revealed that the increased surface expression of these molecules was observed even below the concentration of IFN-γ required for activation of the CAEV LTR (compare Fig. 3B and 4). Increased surface expression of CD64 and MHC class II molecules with 0.1 U of IFN-γ per ml corroborates previously published observations demonstrating that half-maximal stimulation of macrophages in vitro by IFN-γ requires 0.03 U/ml for $H_2O_2$-releasing capacity, 0.14 U/ml for toxoplasma inhibition, and 0.08 U/ml for *Leishmania donovani* killing (20). Thus, activation of the CAEV LTR is not necessarily linked to these events that characterize monocyte differentiation.

To localize a positive element(s) in the CAEV LTR required for the response to IFN-γ in U937 cells, we examined the CAEV LTR (Co isolate) for sequence similarities with binding sites for known transcription factors in a published database, using the FastA algorithm (1). The CAEV LTR has several elements with homology to the activator protein 1 (AP-1) binding site, two copies of a consensus immediate response element for IFN-γ called the gamma-activated site (GAS), one copy of an AP-4 binding site, and a well-conserved TATA box (Fig. 5). Positions −250 to −108 consist of a duplicated 70-bp motif that is not duplicated in the closely related visna virus LTR. A CAAT box and NF-κB sites are not found.

To determine the functional roles of these potential *cis*-acting sites, we constructed a series of 5′ deletions in the CAEV LTR. The wild-type CAEV LTR and 5′ deletions were

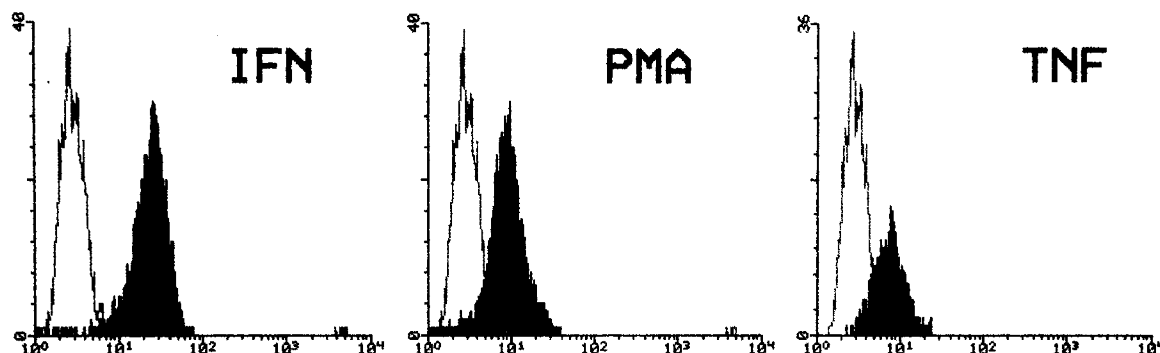


FIG. 2. Flow cytometric analysis of U937 cells. U937 cells were cultivated for 24 h in the absence (open profiles) or presence (shaded profiles) of IFN-γ (200 U/ml), PMA (50 ng/ml), or TNF-α (500 U/ml). Indirect immunofluorescence was performed by exposing $10^6$ cells in a total volume of 250 μl to saturating amounts of a monoclonal antibody directed against MHC class II (CA206) (26) followed by incubation with a fluorescein isothiocyanate-conjugated goat anti-mouse antibody.

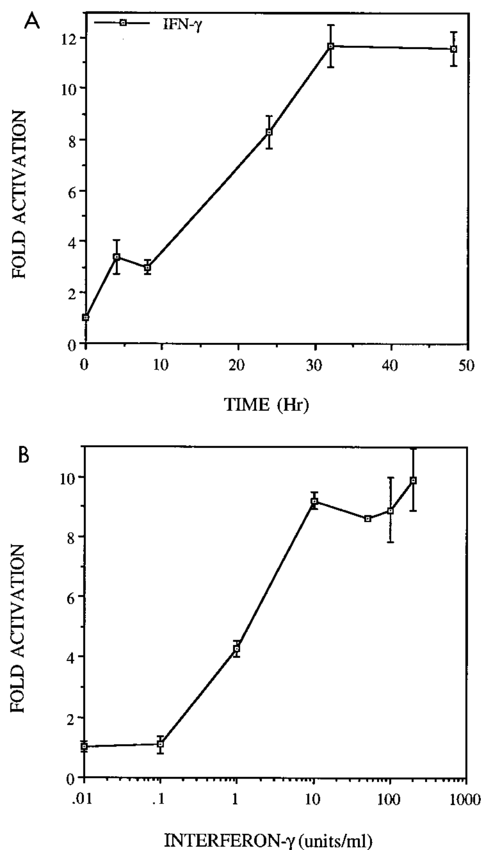


FIG. 3. (A) Time course for activation of the CAEV LTR by IFN-γ. U937 cells were transiently transfected with pCAEV-LTR-CAT (23). Aliquots of cells were stimulated with 200 U of IFN-γ per ml at the indicated times prior to harvesting. Fold activation was calculated as described in the legend to Fig. 1. (B) Dose response of activation of the CAEV LTR by IFN-γ. Aliquots of U937 cells transfected with pCAEV-LTR-CAT were stimulated with the indicated concentrations of IFN-γ 24 h prior to harvesting. Fold activation was calculated as described in the legend to Fig. 1.

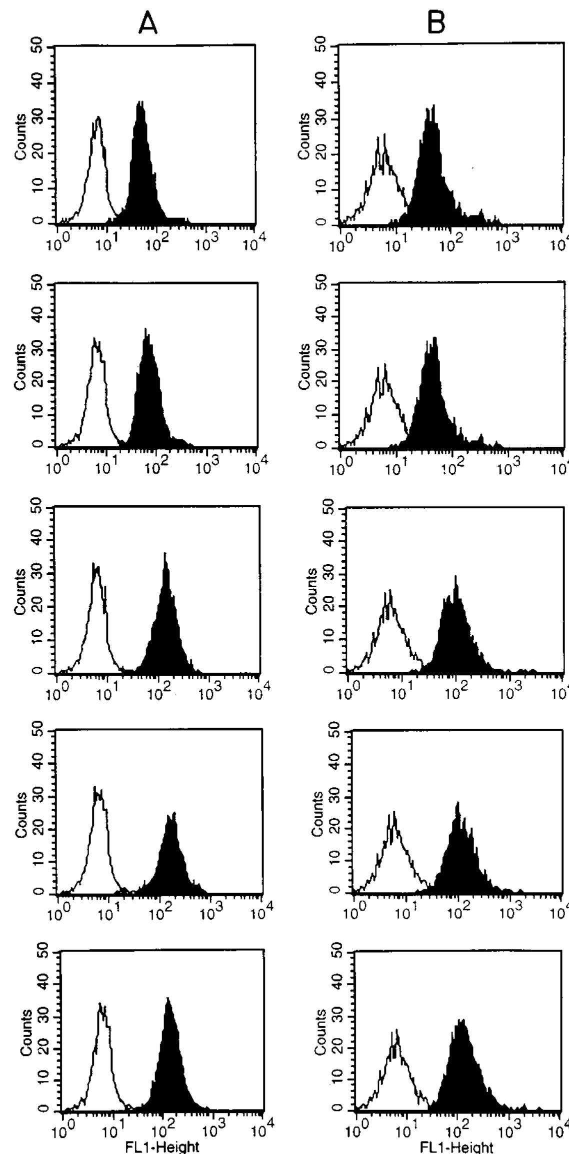


FIG. 4. Activation of U937 cells by IFN-γ. The cells were cultivated for 36 h in the absence (open profiles) or presence (shaded profiles) of different concentrations of IFN-γ (from top to bottom, 0.1, 1, 10, 100, and 1,000 U/ml). Flow cytometric analysis and indirect immunofluorescence were performed as described for Fig. 2. The presence of the cell surface markers CD64 (immunoglobulin receptor FcγRI) (A) and MHC class II molecules (B) was detected by using a monoclonal antibody against FcγRI (mouse anti-human CD64; Serotec, Washington, D.C.) and a monoclonal antibody against MHC class II (CA206) (26), respectively.

subcloned upstream from the CAT reporter gene in pCATbasic. p{−287/+164}CAEVCAT was constructed by PCR amplification of the wild-type CAEV LTR from pCAEV-LTR-CAT and insertion upstream from the CAT gene in the multiple cloning site of pCATbasic. Sequential 5′ deletions were amplified from positions −189 and −107 to position +164 and inserted upstream from the CAT gene in pCATbasic. All plasmid constructions were sequenced throughout the LTR from both directions. Transient transfection of U937 cells showed that deletion to position −189 (p{−189/+164}CAEVCAT) resulted in a 12.0-fold response to IFN-γ. Deletion to position −107 (p{−107/+164}CAEVCAT) resulted in decreased basal activity and eliminated the response to IFN-γ (Fig. 5).

To compare the responses of the CAEV LTR to IFN-γ and PMA, the plasmids containing the sequential 5′ deletions were transfected into U937 cells that were subsequently stimulated with PMA (50 ng/ml). Activation of the wild-type CAEV LTR by PMA results in a 2.4-fold response (Fig. 5). Deletion of one copy of the 70-bp motif in p{−189/+164}CAEVCAT results in 4.7-fold response (Fig. 5). Deletion to position −107, which eliminates both 70-bp repeats, results in 9.8-fold activation (Fig. 5). Thus, activation of the CAEV LTR by PMA requires a region in CAEV LTR that differs from that required by IFN-γ. Deletion to position −107 may remove an inhibitory upstream element and allows activation by downstream elements, such as the AP-1 and AP-4 sites.

To determine whether the 70-bp motif was sufficient for conferring a response to IFN-γ, constructs with one copy (p{−189/−93}tkCAT) and two copies (p{−261/−93}tkCAT) were constructed by PCR amplification of the indicated sequences and insertion upstream from herpes simplex virus thymidine kinase (*tk*) minimal promoter in ptkCAT (29). One copy of the 70-bp motif (positions −189 to −93) contains the GAS element and is sufficient to confer responsiveness to IFN-γ (Fig. 5). Two copies (positions −261 to −93) of the motif increase the basal transcriptional activity of the minimal

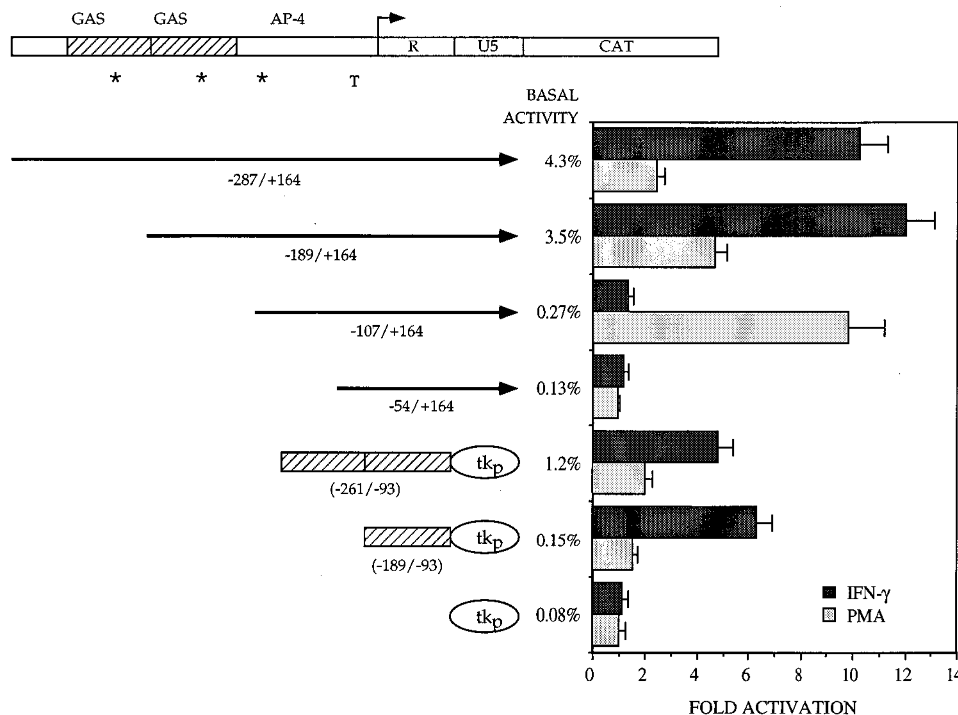


FIG. 5. Mutational analysis of the CAEV LTR. A schematic diagram of CAEV LTR is shown at the top. Duplicated 70-bp motifs are indicated by hatched boxes. Homologies to AP-1 sites (*), the AP-4 site, and GAS elements are shown. T, TATA box. Plasmid constructions containing the indicated 5′ deletions in CAEV LTR were tested in transient transfections of U937 cells. Putative regulatory elements from CAEV LTR were placed upstream from a heterologous promoter, the herpes simplex virus *tk* promoter ($tk_p$) (29), and these plasmids were transfected into U937 cells. Fold activation from IFN-γ (200 U/ml) and PMA (50 ng/ml) in at least three independent transfections is shown.

promoter but result in a response to IFN-γ similar to that observed with a single motif (4.8- and 6.3-fold; Fig. 5).

To determine whether the 70-bp motif could confer a response to PMA, each of the plasmids with one or two copies of this element upstream from the *tk* minimal promoter was transfected into U937 cells that were subsequently stimulated with PMA. The response to PMA was less than 2.0-fold for p{−189/−93}tkCAT and p{−261/−93}tkCAT (Fig. 5). Similar results were obtained with three copies of the 70-bp motif upstream from the *tk* promoter (data not shown). Thus, these data confirm that the regulatory element in the CAEV LTR required for the response to PMA differs from that required for the response to IFN-γ.

Our results demonstrate that the CAEV LTR is activated by IFN-γ and PMA but not by TNF-α or LPS in a promonocytic cell line. The region in the CAEV LTR necessary and sufficient for the response to IFN-γ localizes to positions −189 to −93. This region encompasses one copy of a 70-bp motif which includes a GAS element. Multiple copies of the 70-bp motif increase basal transcription levels but not levels of induction by IFN-γ. Comparison of the dose response of CAEV LTR activation with that of the cellular genes encoding CD64 and MHC class II molecules suggests that LTR activation is not necessarily related to expression of these markers of monocyte differentiation.

Activation of lentiviral LTRs by signaling pathways that lead to monocyte differentiation has been demonstrated for HIV-1, HIV-2, EIAV, and visna virus. Stimulation of monocytes with TNF-α, LPS, or PMA is sufficient to activate the HIV-1 LTR (9, 22). Activation of monocytes with PMA can also activate the HIV-2 (13), EIAV (2), and visna virus (7) LTRs. We observed a small effect of PMA treatment of monocytes on CAEV LTR-directed gene expression. The CAEV LTR is most responsive to stimulation of monocytes with the cytokine IFN-γ. This observation is the first report of regulation of a lentiviral LTR by IFN-γ.

In monocytes stimulated by TNF-α, LPS, and PMA, the second messenger that mediates activation of the HIV-1 LTR is NF-κB, which binds to two sites in the HIV-1 transcriptional enhancer (9, 22). Activation of the HIV-2 LTR during monocyte differentiation requires both NF-κB and members of the *ets* family of proto-oncogenes (13). PU.1, another member of the *ets* family, and AP-1 are transcriptional factors required for optimal expression of EIAV LTR-directed gene expression in mature macrophages (2, 17). FOS-JUN heterodimers that bind to an AP-1 site in the visna virus LTR lead to increased expression of this LTR during activation of monocytes with PMA (25). In contrast, perturbation of the IFN-γ receptor leads to tyrosine phosphorylation of Jak1 and Jak2 (6). These tyrosine kinases activate STAT1α, which translocates to the nucleus and transcriptionally activates several cellular genes (6). The second-messenger pathway stimulated by IFN-γ that leads to activation of the CAEV LTR may be the Jak-STAT pathway. Whether STAT1α binds the CAEV LTR is yet to be determined. The fact that most of the activation of the CAEV LTR occurs after more than 24 h suggests that a newly synthesized protein(s) mediates this effect. Thus, we hypothesize that IFN-γ may lead to phosphorylation and nuclear translocation of STAT1α, which would stimulate new synthesis of a cellular factor that binds to regulatory elements in the LTR and *trans* activates the CAEV promoter. This model would not exclude direct binding of STAT1α to the GAS element in the duplicated 70-bp motif of the CAEV LTR.

In the context of the native promoter, 5′ deletion to position

−189 results in a full response to IFN-γ whereas deletion to position −107 eliminates the response. Deletion to −189 retains one copy of the 70-bp motif and single copies of an AP-1 site, AP-4 site, and TATA box; deletion to position −107 removes the 70-bp motif but retains the latter regulatory elements. In the context of a heterologous promoter, the region in the CAEV LTR that is sufficient to confer a response to IFN-γ lies between positions −189 to −93, which include one copy of the 70-bp motif. Thus, one copy of the 70-bp motif is necessary and sufficient for the response to IFN-γ. The response of p{−189/−93}tkCAT to IFN-γ was about half of that observed with the 5′ deletion to position −189 in the CAEV LTR. This finding suggests that auxiliary response elements in the endogenous CAEV promoter may contribute to a maximal response to IFN-γ.

The response of the 5′ deletions in the CAEV LTR (Co isolate) to stimulation of monocytes with PMA differed from the response with IFN-γ. Deletion to position −107 eliminated the response to IFN-γ but resulted in an increased response to PMA compared with that of the wild-type CAEV LTR, p{−287/+164}CAEVCAT. Further deletion to position −54, which removes all potential elements upstream from the TATA box, eliminates the response to PMA. Thus, elements between positions −107 and −54, such as the AP-1 and AP-4 sites, are necessary for a response to signaling pathways induced by PMA in monocytes. This observation is in agreement with regulation of the visna virus LTR in monocytes, in which stimulation by PMA requires AP-1 sites in this LTR (7).

Our data are in agreement with previous studies of CAEV gene regulation in a primary cell line, tahr ovarian cells. The LTR from CAEV isolate p1244 contains an enhancer region from −182 to −32 (24), which includes AP-1 and AP-4 sites and one copy of the 70-bp motif and GAS. The cellular factors that bind to the 70-bp motif and their interactions with other transcriptional factors, such as AP-1 and AP-4, are yet to be determined.

Our observations are the first report of regulation of a lentiviral LTR by IFN-γ. IFN-γ is an essential cytokine in the immune response of natural killer cells and $Th_1$ subset of T cells to viral infection. The pleiotropic effects of IFN-γ include activation of monocytes into phagocytic cells that attack virally infected targets and an increase in expression of MHC classes I and II. This enhances the function of the macrophage as an antigen-presenting cell (5). We hypothesize that replication of CAEV in immature monocytes occurs at low levels. Subsequent stimulation of natural killer cells and/or $Th_1$ cells by coinfection with other viruses results in release of IFN-γ and activation of monocytes into mature macrophages. These events may thus be a trigger for increased expression of CAEV. Characterization of transcriptional factors that activate the CAEV LTR and are induced by IFN-γ signaling pathways in monocytes will be addressed in future experiments.

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