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Interferons Increase Transcription of a Major Histocompatibility Class I Gene via a 5′ Interferon Consensus Sequence

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Interferons (IFNs) augment expression of major histocompatibility class I genes in many cells. To study the effect of IFNs on transcription of class I genes, we prepared and tested activity of chloramphenicol acetyltransferase (CAT) hybrid genes in which the *cat* gene is under the control of the 5′ flanking region of the murine *H-2L*^{d} gene. NIH 3T3 cells transiently transfected with a *cat* construct having the sequence from position −210 to −134 showed a four- to fivefold increase in CAT activity when treated with IFN-α/β. This sequence contains the IFN consensus sequence (ICS) shared among IFN-inducible genes, as well as the class I regulatory element (CRE) that controls up and down regulation of class I gene expression. To determine the precise sequence requirement for the IFN action, the ICS and CRE were independently placed upstream of the class I or a heterologous simian virus 40 promoter, and CAT activity was tested. The ICS, but not the CRE, enhanced activity of both promoters by about twofold upon exposure to IFN-α/β, although greater responses were noted when the ICS and CRE were combined. These results demonstrate that the ICS alone is capable of enhancing promoter activity in response to IFN-α/β treatment and that the CRE exerts a synergistic effect. Further, we show that the ICS functions as an inducible enhancer since it acts regardless of its orientation and distance in the simian virus 40 promoter.

Interferons (IFNs), potent antiviral agents, induce a number of cellular genes (6, 10, 16, 18, 20, 25, 31) and exert multiple effects upon binding to specific membrane receptors (5, 24). For most genes, induction by IFNs appears to be due to transcriptional activation (10, 11, 18, 21, 31). It has been well documented that both IFN-α/β and IFN-γ increase expression of major histocompatibility (MHC) class I transplantation antigens (2, 9, 10, 25; F. M. Rosa, M. M. Cochet, and M. Fellows, *in* I. Gresser, ed., *Interferon 7*, in press). Augmentation of class I antigen expression correlates with an increase in steady-state levels of the corresponding mRNA (35). IFNs also induce class I gene expression in early embryos (23) and in neuronal cells (37), in which class I antigen expression is absent.

It has been indicated that IFNs increase MHC class I gene expression by acting on sequences within or in close proximity to the genes, since human and porcine MHC class I genes introduced into mouse cells increase their expression when treated with IFNs (25, 27, 39). Consistent with this assumption, Vogel et al. (34) reported that promoter activity of a mouse class I gene is upregulated by IFNs via a 350-base-pair (bp) 5′ flanking sequence. In addition, Baldwin and Sharp (1) showed that IFN enhances activity of a cat gene controlled by a 190-bp 5′ flanking sequence of the murine *H-2K*^{b} gene but not by a 138-bp 5′ sequence of the gene. These reports indicate that IFN activates transcription of MHC class I genes. Friedman and Stark (11) found the presence of an about 30-bp IFN consensus sequence (ICS) in the 5′ flanking region of some IFN-inducible genes and suggested that it is involved in regulating expression of IFN-inducible genes. Sequences homologous to the proposed ICS have been found in a number of mouse class I genes (17). The ICS directly juxtaposes and partially overlaps with the class I regulatory element (CRE) that regulates class I gene expression in a developmentally controlled fashion (22). Recently, Israel et al. (15) reported that the ICS is effective in enhancing class I promoter activity by IFN only in association with a functional CRE.

IFNs enhance promoter activity of the *H-2L*^{d}*-cat* gene introduced into NIH 3T3 cells. To assess the contribution of the 5′ flanking region of the *H-2L*^{d} gene to IFN-induced augmentation of class I gene expression, we tested the chloramphenicol acetyltransferase (CAT) activity of pL^d-cat392, in which transcription of the *cat* gene is directed by the 5′ flanking region of the *H-2L*^{d} gene (8) (from position −392 to +14 relative to the cap site) (see Fig. 2A). After transient introduction of the constructs (1 μg of *cat* DNA plus 19 μg of carrier DNA, pUC19) into NIH 3T3 cells by the calcium phosphate precipitation method (14), cells were treated with increasing concentrations of INF-α/β or IFN-γ for 44 h (Fig. 1A). IFN-α/β was purchased from Lee Biomolecular, and recombinant IFN-γ was a gift from Shionogi Research Laboratories, Osaka, Japan. The titers were determined by the previously described method (38). pL^d-cat392 gave significant CAT activity without IFN treatment, as expected, since class I genes are constitutively expressed in NIH 3T3 cells. The promoterless *cat* gene in plasmid pSVO-cat gave negligible CAT activity. Treatment of the cells with IFN-α/β resulted in enhancement of CAT activity in a dose-dependent manner. Maximum enhancement was seen at 1,000 U of IFN-α/β per ml, when CAT activity was about six times higher than in the untreated control. In accordance, the level of surface expression of MHC class I antigens was enhanced about threefold in NIH 3T3 cells by IFN-α/β at this dose (see Fig. 5). IFN-γ enhanced CAT activity only modestly (about twofold), and dose dependence was not detected up to 1,000 U of IFN-γ per ml. Elevation of CAT activity by IFNs was specific for pL^d-cat392 since the *cat* construct under control of the chicken actin promoter (28) did not exhibit elevated CAT activity even at 1,000 U of IFN-α/β per ml (Fig. 1A). The effect of IFNs was also tested after stable introduction of

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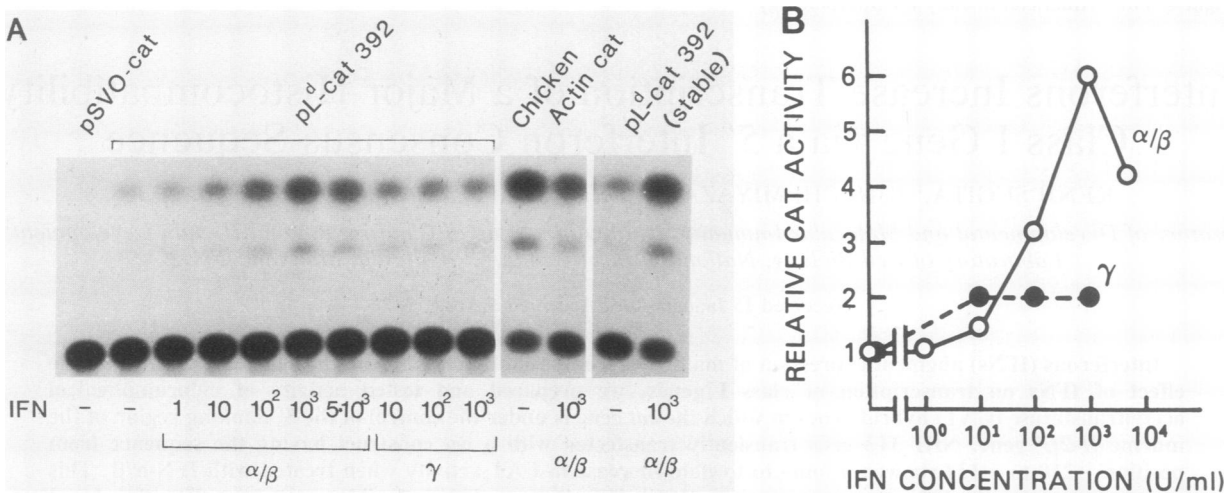

FIG. 1. Enhanced promoter activity of the *H-2L^d-cat* hybrid gene after IFN treatment. (A) *cat* constructs (1 μg each) were transiently introduced into NIH 3T3 cells together with carrier DNA (14). After transfection, cells were incubated with IFN-α/β or INF-γ at the indicated concentrations for 44 h. Stably transformed cells expressing pL^d-cat392 (two right lanes) were incubated with IFN-α/β (1.000 U/ml) for 72 h, and CAT activity was tested as previously described (12, 13). (B) Amounts of acetylated [^{14}C]chloramphenicol detected in the autoradiograph of pL^d-cat392 were measured, and the levels of enhancement in CAT activity relative to the untreated control (taken as 1) were plotted.

pL^d-cat392 into NIH 3T3 cells by using pSV2-neo as a selectable marker (30). Most of the colonies that arose after selection were pooled to obtain unbiased values of average CAT activity and treated with IFN-α/β for 72 h. IFN treatment caused a fourfold increase in CAT activity (Fig. 1A), showing that a sequence involved in enhancement of class I promoter activity is located within the about 400-bp 5′ flanking sequence of the *H-2L^d* gene and that the same regulation occurs in the *cat* gene regardless of whether the gene is expressed transiently or after integration into the host chromosome.

Analyses of deletion constructs. To localize further the sequence involved in enhancing MHC class I promoter activity upon IFN-α/β treatment, various deletion constructs were prepared and tested (Fig. 2A and C). Two deletion constructs, pL^d-cat237 and pL^d-cat210, showed enhanced CAT activities upon IFN-α/β treatment, the level of enhancement was equivalent to that caused by pL^d-cat392. Thus, the site of IFN action maps downstream of position −210. Since no CAT augmentation was found with pL^d-catdel5, in which the sequence between −342 and −134 was deleted, the site in question may reside within this region or encompass position −134. This localization is in agreement with reports by Baldwin and Sharp (1) and Israel et al. (15). The sequence from −210 to −134 is highly conserved among mouse class I genes (17) and contains the CRE (17, 22) and the ICS (11) (Fig. 2B). To determine whether the IFN-induced effect is elicited by either of the two sequences, two additional constructs were prepared in which synthetic oligonucleotides corresponding to the CRE or the ICS were connected to the *Ava*II-*Bam*HI fragment (−123 to +14) of the 5′ flanking region of the *H-2L^d* gene (Fig. 2). The *Ava*II-*Bam*HI fragment alone connected to the *cat* gene (pL^d-cat123) gave no enhancement after IFN-α/β treatment. Similarly, pL^d-cat123CRE, which contains the CRE, did not respond to IFN treatment. In contrast, pL^d-cat123ICS, which contains the ICS alone, showed a twofold increase in CAT activity (Fig. 2A and C). The enhancement by pL^d-cat123ICS was highly reproducible, the standard deviation of three experiments being less than 20%. It is of note, however, that the level of enhancement by this construct was consistently lower than that seen by pL^d-cat210 or pL^d-cat237, suggesting that the juxtaposed CRE potentiated the CAT enhancement mediated by the ICS (15).

The ICS confers ability to respond to IFNs on a heterologous promoter. To delineate how the ICS enhances transcription of the MHC class I gene, *H-2L^d* fragments containing the ICS were connected to a simian virus 40 (SV40) promoter fused with the *cat* gene (14), and CAT activity was measured in NIH 3T3 cells after IFN-α/β treatment (Fig. 3). The 72-bp repeat enhancer sequence present upstream of pSV2-cat was removed, and the *H-2L^d* fragments were placed in either the native or the reverse orientation (Fig. 3). Neither pSV2-cat nor the enhancerless pSV-catdelE responded to IFN treatment. Placement of the *H-2L^d* fragment from −392 to −121 in front of the SV40 promoter in the native orientation (pLS-cat*c1*) increased CAT activity 3.2-fold after IFN-α/β treatment. When a shorter fragment (−210 to −121) was connected to the SV40 promoter, IFN-α/β treatment caused a similar level of increase in CAT activity, which was observed regardless of the orientation (pLS-catc2 and pLS-catr2 in Fig. 3). The ability of the ICS to enhance promoter activity was also tested in the SV40 promoter (pLS-catICS and pLS-catCRE in Fig. 3). As with the *H-2L^d* promoter, the ICS, but not the CRE, gave significant enhancement of CAT activity upon treatment with IFN-α/β. These results indicate that the ICS alone is capable of conferring IFN responsiveness to a heterologous promoter. Moreover, the ICS is apparently capable of acting independently of its orientation.

Analysis of transcription initiation sites by primer extension. To confirm that the *H-2L^d-cat* and SV40 constructs studied here initiated *cat* mRNA synthesis at the correct start sites, primer extension experiments were performed. Total RNA was prepared by the method of Chirgwin et al. (7) from the cells transfected with pL^d-cat392 or pLS-catICS with or without IFN-α/β treatment. RNA (20 μg) was hybridized with about 3 ng of ^{32}P end-labeled 26-mer oligonucleotide 5′CTCCATTTTAGCTTCCTTAGCTCCTG-3′, which is complementary to the 5′ end of the coding region of the *cat* gene, and an extension reaction was carried out as previously described (22). With RNAs prepared from the pL^d-cat392 transfection, the ^{32}P-labeled primer was ex-

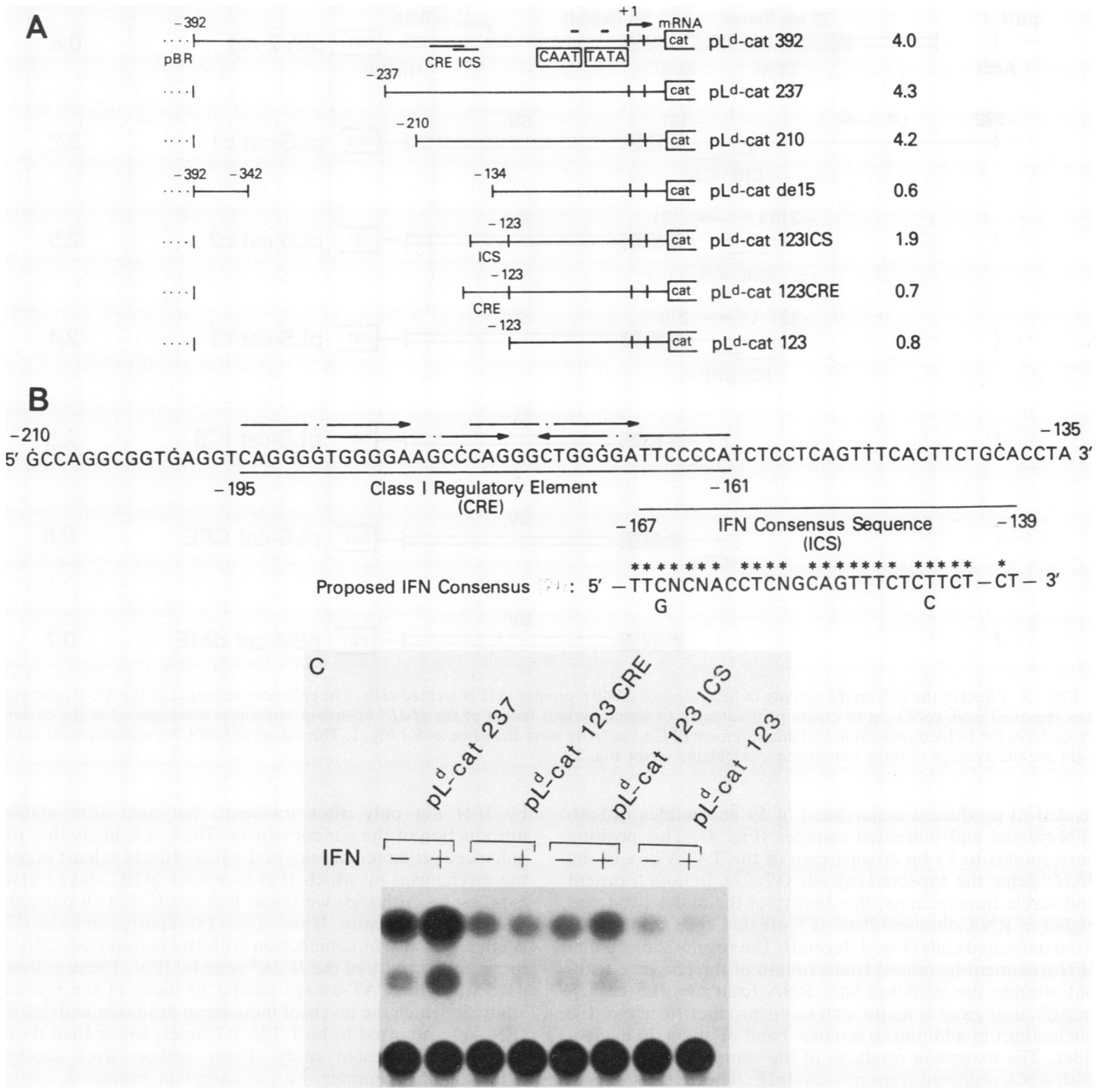

FIG. 2. The role of ICS in enhancement of class I promoter activity by IFN treatment. (A) Schematic representation of *H-2L*^{d} constructs containing the ICS, CRE, or deletions. CAT and TATA represent CAT (CCAATC) and TATA (TATAAA) boxes of the *H-2L*^{d} gene (negative number represents nucleotide end position relative to the cap site shown as +1). The oligonucleotides corresponding to the CRE and the ICS, respectively, used in this study were as follows:

```
5' GATCT GTCAGGGGTGGGGAAGCCCAGGGCTGGGGATTCCCATC GCATG 3'
3'   A  CAGTCCCCACCCCTTCGGGTCCCGACCCCTAAGGGTAG C 5'
BglII                                            SphI

5' GATCT GATTCCCCATCTCCTCAGTTTCACTTCTGCACC GCATG 3'
3'   A  CTAAGGGGTAGAGGAGTCAAAGTGAAGACGTGG C 5'
BglII                                      SphI
```

The boxed sequences represent restriction sites with which new oligonucleotides were inserted into appropriate plasmids. Transient introduction of these constructs and measurements of CAT activity were carried out as for Fig. 1. The values of fold CAT enhancement on the right are the average of three experiments and represent the CAT activity of cells treated with IFN-α/β (1,000 U/ml) divided by the CAT activity of untreated cells. (B) DNA sequence of the CRE and the ICS of the *H-2L*^{d} gene. The ICS proposed by Friedman and Stark (11) is shown below (asterisks represent positions of nucleotide homology in the *H-2L*^{d} gene). (C) Autoradiograph of CAT activity by pL^d-cat123ICS enhanced upon IFN treatment.

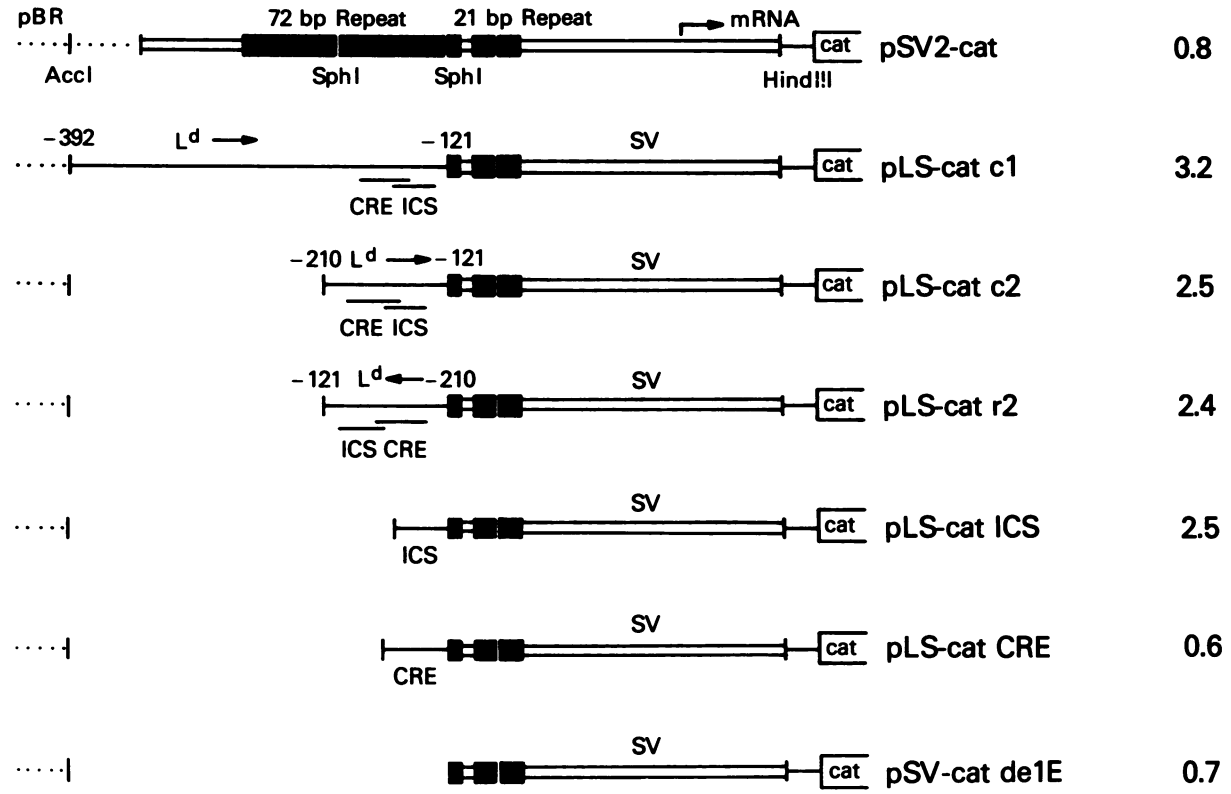

FIG. 3. Effect of the ICS on the activity of heterologous SV40 promoter in IFN-treated cells. The enhancer sequence of the SV40 promoter was removed from pSV2-cat to create pSV-catdelE, to which various length of the *H-2L*^{d} upstream sequences were placed at the 5′ end. Procedures for DNA transfection and measurement of CAT activity were the same as for Fig. 1. The values of fold CAT enhancement at the right are the average of three experiments calculated as for Fig. 2.

tended to produce a major band of 59 nucleotides in both IFN-treated and untreated samples (Fig. 4). This position corresponds to 23 bp downstream of the TATA box of the *H-2L*^{d} gene, the expected cap site (17, 22). In both transient and stable transfections, the density of the major band was higher in RNA obtained from IFN-treated cells than in that from untreated cells (Fig. 4, legend). The results showed that IFN treatment increased transcription of the *cat* gene without altering the initiation site. RNA from the pLS-catICS transfection gave a major extension product of about 100 nucleotides in addition to a minor band of about 70 nucleotides. The extension products of the same size were noted with RNA prepared from pSv-catde1E. These results are in accordance with the transcription initiation site of the pSV2-cat reported by Gorman et al. (13). Again, RNA from IFN-treated pLS-catICS exhibited a much denser major band than that of untreated cells, which indicates that IFNs elevate the levels of *cat* mRNAs transcribed from the SV40 promoter under the influence of the ICS.

We show that IFNs enhance promoter activity of the *H-2L*^{d} gene and that the highly conserved ICS in the 5′ flanking region is responsible for conferring the responsiveness to IFN-α/β. The presence of the ICS was first reported by Friedman and Stark (11) on the basis of homology of IFN-inducible genes, without functional verification, however. We found that the ICS acts as an inducible enhancer (3, 19, 29) since it is capable of conferring IFN-induced enhancement on the SV40 promoter irrespective of its orientation, although the degree of enhancement by IFN is modest. We also show that the promoter activity is increased by IFN not only after transient, but also after stable, introduction of the *cat* constructs. Thus, it is likely that the enhanced promoter activity of the ICS reflects at least in part the mechanism by which IFN increases MHC class I gene expression. Although we found that the ICS is an independent functional entity, Israel et al. (15) reported that the ICS is effective only in conjunction with the juxtaposed CRE in increasing activity of the *H-2K*^{b} gene by IFN. These authors used transient CAT assays similar to those of the present study, in which the levels of increase in promoter activity by IFN were reported to be 1.7 to 2.7 times, lower than those found in the present study. These authors used another heterologous promoter, i.e., conalbumin promoter, rather than the native MHC class I gene or SV40 promoter used in the present paper. The use of different promoters may be the cause of the discrepancy, as conalbumin may have obscured the activity of the ICS. In addition, a possible difference in transfection efficiency may have caused the different results. At present, we cannot exclude other factors, such as concentrations of IFN or use of different cells. It is of note that in our study also the presence of the CRE, which is by itself ineffective in response to IFN, however, heightened the levels of CAT enhancement for the class I promoter (Fig. 2), illustrating synergistic effects elicited by the CRE.

It is not clear how general the presence of ICS and its functions are among various IFN-inducible genes, many of which are transcriptionally regulated by IFNs (10, 11, 18, 21, 31, 33). Recently, Boss and Strominger (4) identified an upstream sequence required for MHC class I gene induction by IFN-γ, which does not exhibit homology to the ICS,

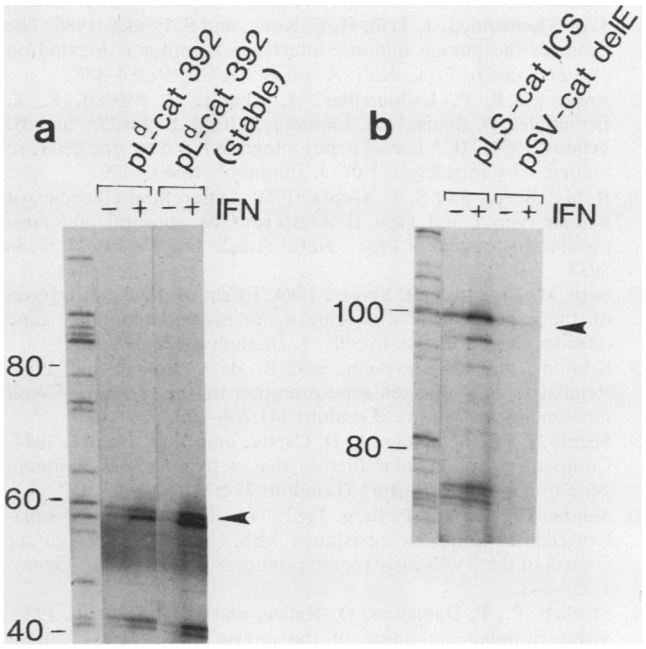

FIG. 4. Analysis of transcription start sites by primer extension. (a) Total RNA was prepared after transient or stable transfection of NIH 3T3 cells with pL^d-cat392 with (+) or without (−) IFN-α/β treatment (1,000 U/ml) for 36 or 48 h. (b) RNA from pLS-catICS or pSV-catdelE transfection was tested. Primer extension was carried out as described in the text. The left lane in each panel represents adenosine or cytosine residues of the pL^d-cat392 sequence. Densitometry analyses of the RNA bands indicated 3.6- and 8.1-fold increases caused by IFN treatment in transient and stable transfections, respectively, of pL^d-cat392, (a). pLS-catICS showed a 2.8-fold increase (b). The numbers to the left of each panel indicate size in nucleotides, and the arrowheads on the right indicate the start site.

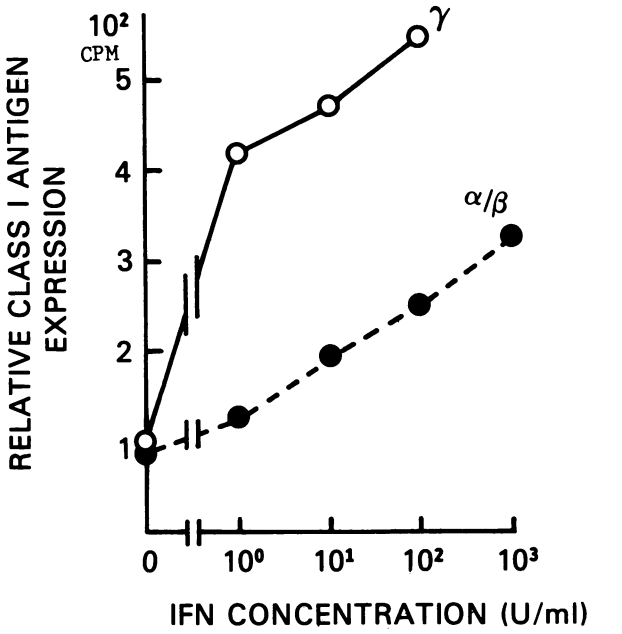

FIG. 5. Effect of IFN-α/β and IFN-γ on expression of surface MHC class I antigens. NIH 3T3 cells incubated in a 96-well microtiter plate were treated with IFNs for 72 h. The antigens expressed on the surface were detected by binding of rat monoclonal antibodies against mouse MHC class I antigens (42.3.9.8 and K204) (23) followed by binding of ^{125}I-labeled sheep anti-rat immunoglobulin (Amersham Corp., Arlington Heights, Ill.). Each value represents the average of triplicate measurements.

indicating involvement of other sequences in response to IFNs.

It should be noted that our study did not exclude the possibility that mechanisms other than those found in this study are involved in increasing class I gene expression by IFNs. Additional mechanisms may play a predominant role, particularly in response to IFN-γ, with which at most a twofold increase in CAT activity was seen (Fig. 1). No measurable increase was detected with the construct containing the ICS alone in transient CAT assays (data not shown). Paradoxical to the low degree of CAT enhancement, surface expression of class I antigens in NIH 3T3 cells was found to be enhanced to a greater degree by IFN-γ than by IFN-α/β (Fig. 5). The dichotomy of the actions of INF-γ and IFN-α/β may not be surprising since they act through distinct membrane receptors (5, 24) and elicit distinct functional properties (26, 33, 36). The effect of IFN-γ on MHC class I gene expression may be in part mediated by introns or the 3′ region of the gene. In support of this notion, preliminary experiments suggested that replacement of the promoter region of the *H-2L^d* gene with the SV40 promoter results in higher surface expression of the *H-2L^d* antigen upon IFN-γ treatment as tested in stable transformants (unpublished data). It is conceivable that the effect of INF-γ is predominantly at the level of posttranscriptional regulation.

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