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# Characterization of the promoter of the human gene encoding the high-affinity IgG receptor: Transcriptional induction by γ-interferon is mediated through common DNA response elements

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ABSTRACT **Expression of the high-affinity receptor for IgG ($Fc_\gamma RI$) is restricted to cells of myeloid lineage and is induced by γ-interferon (IFN-γ) but not by IFN-α/β. The organization of the human $Fc_\gamma RI$ gene has been determined and the DNA elements governing its cell type-restricted transcription and IFN-γ induction are reported here. A 39-nucleotide sequence (IFN-γ response region, or GRR) is defined that is both necessary and sufficient for IFN-γ inducibility. Sequence analysis of the GRR reveals the presence of promoter elements initially defined for the major histocompatibility complex class II genes: i.e., X, H, and γ-IRE sequences. Comparison of a number of genes whose expression is induced selectively by IFN-γ indicates that the presence of these elements is a general feature of IFN-γ-responsive genes. Our studies suggest that the combination of X, H, and γ-IRE elements is a common motif in the pathway of transcriptional induction by this lymphokine.**

Interferons (IFNs) mediate antiviral and immune responses and stimulate cell growth and differentiation through transcriptional activation of IFN-responsive genes (reviewed in ref. 1). Two types of IFNs have been described, type I (IFN-α/β) and type II (IFN-γ). Both act through type-specific cell surface receptors to induce the expression of unique, although overlapping, sets of genes. Genes that are induced only by IFN-α/β, such as ISG15 and ISG54, or by both IFN-α/β and IFN-γ, such as the guanylate-binding protein (GBP) and major histocompatibility (MHC) class I genes, appear to share a common mechanism for transcriptional regulation, which is mediated by a conserved sequence, termed the IFN-stimulated response element (ISRE) (2–6). Interaction of IFN-α/β with its receptor activates a positive regulatory factor, ISGF3, that binds to the ISRE (7). IFN-γ can enhance this effect by stimulating the synthesis of the DNA-binding subunit of ISGF3 (8). An additional element overlapping the ISRE has been identified in the GBP promoter (4, 9). Termed the gamma-activated sequence (GAS), this element contributes to both IFN-α/β and IFN-γ transcriptional activation by binding distinct trans-acting factors.

In contrast, a common mechanism of transcriptional induction has yet to be established for genes that are responsive to IFN-γ but not to IFN-α/β. Included in this set are genes encoding IP-10, monokine induced by IFN-γ (MIG), macrophage inhibitory protein 2, MHC class II antigens, the MHC class II-associated invariant chain, and the high-affinity receptor for IgG ($Fc_\gamma$ receptor type I, $Fc_\gamma RI$) (10–15). Among the cis-acting elements shown to mediate the IFN-γ activation of these genes are the ISRE of the invariant-chain gene promoter and the X, H, and γ-IRE sequences of MHC class II gene promoters (16–21). We are interested in determining the mechanisms by which IFN-γ is able to regulate the immune response, and have focused our work on the DNA elements responsible for the transcriptional induction of the human $Fc_\gamma RI$ gene.

$Fc_\gamma RI$ belongs to the family of immunoglobulin-like cell surface receptors that bind the Fc region of IgG and are capable of triggering antibody-dependent cellular cytotoxicity, phagocytosis, and the respiratory burst (reviewed in ref. 22). $Fc_\gamma RI$ expression is restricted to cells of myelomonocytic origin and is enhanced by exposure to IFN-γ, but not IFN-α/β. This enhanced expression in response to IFN-γ reflects an increase in the rate of $Fc_\gamma RI$ transcription that is independent of protein synthesis (R. Pine and J. Darnell, personal communication; refs. 23 and 24). $Fc_\gamma RI$ thus represents a prototypical IFN-γ-responsive gene whose induction results in augmentation of the innate immune response.

In this paper we present the structure of the gene encoding human $Fc_\gamma RI$ (hu$Fc_\gamma RI$),† focusing on the structure of its promoter and characterization of the DNA sequences responsible for its induction by IFN-γ. A 39-base-pair (bp) cis-acting region, termed the IFN-γ response region (GRR), is shown to be responsible for IFN-γ induction and to be sufficient to confer pronounced IFN-γ inducibility upon a heterologous promoter. The GRR contains elements homologous to those defined for MHC class II promoters and several other IFN-γ-responsive genes, indicating that, as in the case of IFN-α/β-responsive genes, common sequence motifs are involved in transcriptional activation of this class of genes.

## MATERIALS AND METHODS

**Genomic Cloning.** Genomic clones were isolated from two libraries made with either human placental or A/J mouse DNA cloned into cosmid vectors.

**Plasmid Constructions.** p(−1000)TK was made by cloning hu$Fc_\gamma RI$ genomic sequence from −1039 to +113 into the *Sal* I site of pTKCAT (25). p(−1000)CAT was made by cloning the same insert into the promoterless chloramphenicol acetyltransferase (CAT) expression vector p(TKO)CAT (25). GRR MINUS was made by cloning hu$Fc_\gamma RI$ genomic sequence from −1039 to −58 into the *Hin*dIII site of the 5′ deletion clone p(−18)CAT. p(GRR)TK was made by cloning hu$Fc_\gamma RI$ genomic sequence from −57 to −18 into the *Sal* I site of pTKCAT. All inserts were generated by standard PCR techniques using cosmid clone 8830 as template. The 5′

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Abbreviations: IFN, interferon; ISRE, IFN-stimulated response element; GRR, IFN-γ response region; $Fc_\gamma RI$, $Fc_\gamma$ receptor type I; hu, human; mu, murine; MHC, major histocompatibility complex; MIG, monokine induced by IFN-γ; CAT, chloramphenicol acetyltransferase; TK, thymidine kinase.

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†The sequences reported in this paper have been deposited in the GenBank data base [accession nos. M82819 (hu$Fc_\gamma RI$) and M82818 (mu$Fc_\gamma RI$)].

deletions of p(−1000)CAT were made by exonuclease III digestion (26).

**DNA Transfection.** Transfection of U-937 and RAW264.7 cells was performed as described by Wright and Farber (27), and transfection of HeLa S3 cells was as described by Golub *et al.* (28). After transfection, cells were allowed to recover for 48 hr and then treated with IFN, harvested (29), and analyzed for β-galactosidase activity (26). CAT assays were performed (26) on extracts containing equivalent β-galactosidase activity.

## RESULTS

**Organization and Sequence of the huFc$_\gamma$RI Gene.** Twelve overlapping clones were isolated from a human cosmid library by using a probe derived from huFc$_\gamma$RI cDNA clone p135 (30). A restriction map generated from those clones is shown in Fig. 1*A*. The restriction fragments obtained from those clones comigrated with genomic DNA cut with the same enzymes (data not shown). The huFc$_\gamma$RI gene consists of six exons distributed over 10 kb and is organized similarly to other members of the FcR gene family. An 11-kb region spanning this gene has been completely sequenced. The sequences surrounding the intron/exon junctions conform to the consensus sequences for splice junctions, and are highly homologous to the corresponding sequences found in the other Fc$_\gamma$R genes (31–33).

Five sites of RNA initiation were determined by primer extension using RNA from IFN-γ-treated U-937 and HL-60 cells (Fig. 2*A*). The major initiation site (position +1) in U-937 cells is 113 bp 5′ of the ATG codon, with a second prominent site 58 bp 5′ of the ATG. In HL-60 cells all five sites appear to be used equally. These sites of RNA initiation were consistent among experiments using different end-labeled primers and were confirmed by RNase protection (Fig. 2*B*). Similar initiation sites have been found by van de Winkel *et al.* (34). A 1-kb sequence including these initiation sites and upstream region is shown in Fig. 1*B*.

**Sequence of the Murine Fc$_\gamma$RI (muFc$_\gamma$RI) Promoter.** Six clones containing the muFc$_\gamma$RI gene were isolated from a murine cosmid library by using a probe derived from muFc$_\gamma$RI cDNA clone D13-3 (35). These clones were digested with restriction enzymes, mapped, and sequenced. Comparison of the huFc$_\gamma$RI and muFc$_\gamma$RI promoter sequences reveals significant conservation in the regions encompassing the promoters of these genes (Fig. 1*C*).

**IFN-γ Inducibility and Cell-Type Specificity Demonstrated by 1.1 kb of huFc$_\gamma$RI Promoter.** To define the promoter region of the huFc$_\gamma$RI gene, a reporter plasmid was constructed using huFc$_\gamma$RI upstream sequence from −1039 to +113 fused to the promoterless bacterial CAT gene. This construct, p(−1000)CAT, was transfected into myeloid and fibroblastic cells of both mouse and human origin. Cotransfection with pSV-β-galactosidase control plasmid (Promega) was used to equalize transfection efficiencies among experiments. p(−1000)CAT was induced by IFN-γ, but not by IFN-α, in both the human monocytic cell line U-937 and the murine macrophage line RAW264.7 (Fig. 3). To ensure the competency of the cell's response to IFN-α, RAW264.7 cells were transfected with a construct, GBP-CAT, known to be IFN-α inducible (4). Expression of this construct was induced by IFN-α at 100 units/ml (Fig. 3, control).

p(−1000)CAT and GBP-CAT were also transfected into the human cervical carcinoma cell line HeLa S3. HeLa cells did not express p(−1000)CAT, but did express GBP-CAT control, after IFN-γ induction (Fig. 3). Thus, the normal pattern of cell-type restriction and interferon specificity

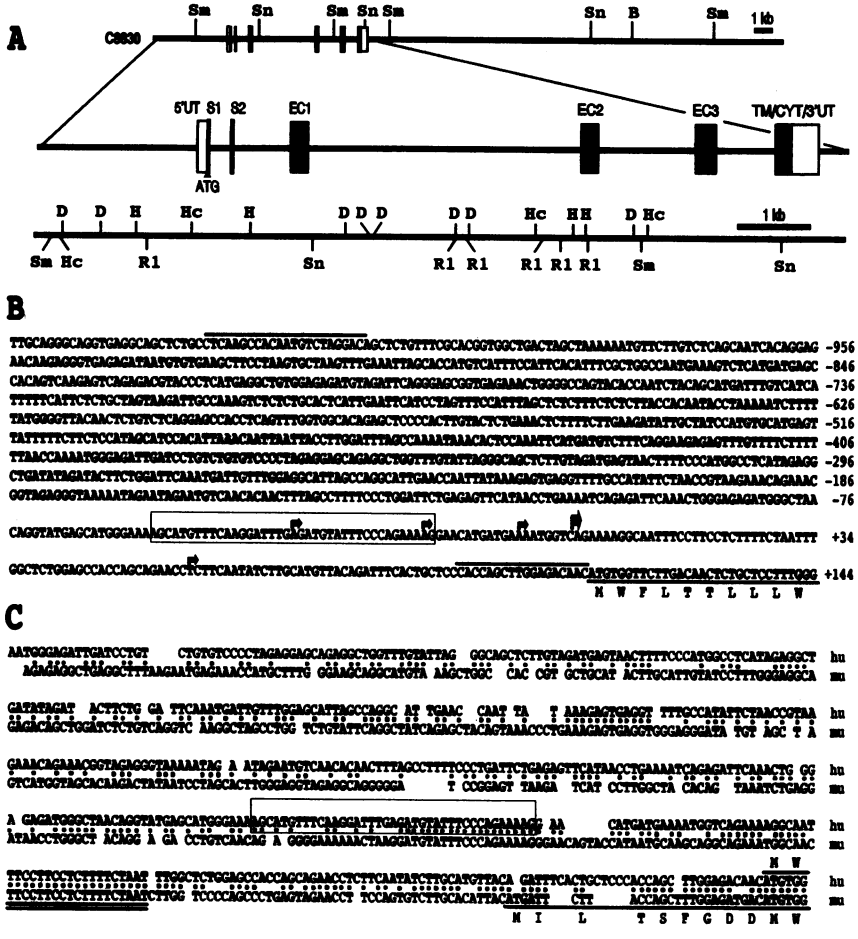


FIG. 1. Genomic structure and promoter region of the huFc$_\gamma$RI gene. (*A*) Physical map. B, *Bam*HI; D, *Dra* I; Hc, *Hin*cII; H, *Hin*dIII; R1, *Eco*RI; Sm, *Sma* I; Sn, *Sna* I; 5′UT, 5′ untranslated domain; S1, first signal exon; S2, second signal exon; EC1, first extracellular exon; EC2, second extracellular exon; EC3, third extracellular exon; TM, transmembrane domain; CYT, cytoplasmic domain; 3′UT, 3′ untranslated domain; kb, kilobase. (*B*) Nucleotide sequence of the 5′ flanking region. The first signal exon is underlined and translated. The five sites of RNA initiation, as determined by primer extension and RNase protection (see Fig. 2), are indicated by arrows; the major site (position +1) is shown by a large arrow. Overlines indicate the two oligonucleotides used in the making of p(−1000)CAT and p(−1000)-TK. The GRR is boxed. (*C*) Comparison of the human (hu) and murine (mu) Fc$_\gamma$RI promoters. The start of the first signal exon is overlined for the huFc$_\gamma$RI gene and underlined for the muFc$_\gamma$RI gene. The GRR for the huFc$_\gamma$RI promoter is boxed. A second region of homology 3′ to the GRR is doubly underlined.

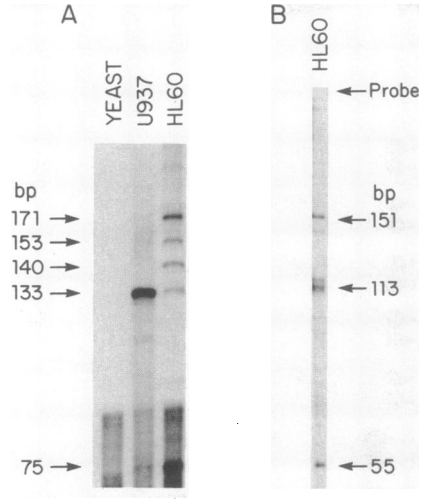


FIG. 2. Mapping of the RNA initiation sites of the huFc$_\gamma$RI gene. Total cellular RNA was isolated from U-937 and HL-60 cells pretreated for 6 hr with recombinant human IFN-$\gamma$ at 200 units/ml. (*A*) Primer extension was performed (26) using 40 $\mu$g of total RNA hybridized at 40°C to a $^{32}$P-end-labeled oligonucleotide complementary to nucleotides +113 to +133 within the huFc$_\gamma$RI genomic sequence. Yeast total RNA served as a control. Shown is the autoradiograph of the primer-extended products analyzed in an 8% polyacrylamide sequencing gel. Identical start sites were obtained using a second $^{32}$P-end-labeled oligonucleotide complementary to nucleotides +93 to +113 (data not shown). (*B*) RNase protection analysis was performed (26) using an antisense RNA probe complementary to the huFc$_\gamma$RI sequence from −311 to +113. The probe was allowed to hybridize overnight at 45°C to 20 $\mu$g of total cellular RNA from either yeast or IFN-$\gamma$-treated HL60 cells; it was then digested with RNase A and RNase $T_1$ for 1 hr at 30°C. Shown are the RNase-resistant bands analyzed in an 8% sequencing gel. The protected bands at 151, 113, and 55 bp correspond to initiation sites determined by primer extension.

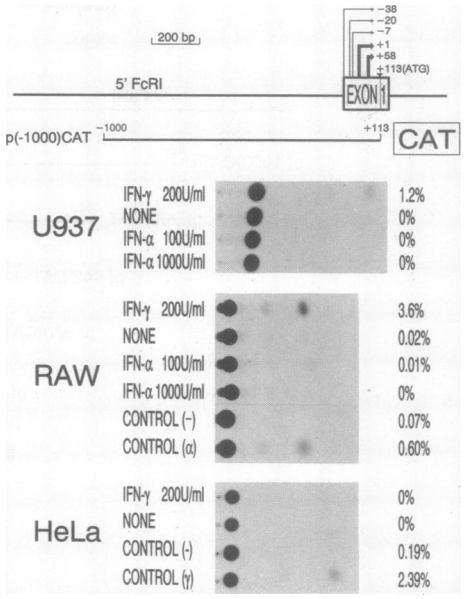


FIG. 3. Activity of the huFc$_\gamma$RI promoter after transfection into myeloid and non-myeloid cell lines. The structure of the reporter construct p(−1000)CAT is shown below the corresponding 5′ region of the huFc$_\gamma$I gene. The 5′ and 3′ oligonucleotides used to generate the p(−1000)CAT insert are indicated by overlines in Fig. 1*B*. Representative CAT activities after transfection of p(−1000)CAT into U-937, RAW264.7, and HeLa S3 cells are shown along with percent conversion of [$^{14}$C]chloramphenicol. CONTROL indicates transfection with GBP-CAT: (−) indicates no cytokine treatment; ($\alpha$) indicates treatment with recombinant human IFN-$\alpha$ at 200 units (U)/ml; ($\gamma$) indicates treatment with recombinant human IFN-$\gamma$ at 100 U/ml. CAT activities after transfection of p(TKO)CAT into U-937, RAW264.7, and HeLa S3 cells were undetectable, with or without IFN-$\gamma$ treatment.

could be recapitulated with 1.1 kb of sequence derived from the huFc$_\gamma$RI gene upstream region.

**Localization of the GRR in the Fc$_\gamma$RI Promoter.** A series of 5′ deletion mutants of p(−1000)CAT were tested for their ability to respond to IFN-$\gamma$. A representative experiment in U-937 cells is shown in Fig. 4. In both U-937 and RAW cells, the property of induction by IFN-$\gamma$ remained constant for all deletion mutants containing at least 57 bp of 5′ flanking sequence and the 113 bp of untranslated exon 1. When a further 39 bp of 5′ flanking sequence was deleted, IFN-$\gamma$ inducibility was lost. Instead, constitutive expression was observed at a level comparable to that achieved after IFN-$\gamma$ induction. This property of high constitutive expression continued in mutants with more extensive 5′ deletions, until the last transcription start site was deleted, whereupon all expression ceased. None of the deletion mutants was expressed when transfected into HeLa S3 cells.

These results suggest that the promoter elements that confer IFN-$\gamma$ inducibility lie within a 39-bp sequence from −57 to −18, which we have termed the GRR. They also suggest that the GRR is able to repress constitutive expression. To test this, a construct, GRR MINUS, was made in which the GRR was deleted from p(−1000)CAT. With or without IFN-$\gamma$ treatment, there was no expression of GRR MINUS when transfected into either RAW or U-937 cells (Fig. 4), confirming that the GRR is necessary to confer IFN-$\gamma$ inducibility. The lack of IFN-$\gamma$ induction of GRR MINUS was expected, but the lack of constitutive expression was not, and suggests that elements 5′ to the GRR also serve to control constitutive expression.

**A 39-bp Fragment from the Fc$_\gamma$RI Promoter Confers IFN-$\gamma$ Responsiveness on a Heterologous Promoter.** To examine whether the GRR could mediate IFN-$\gamma$ induction of a heterologous promoter, the GRR was cloned upstream to the thymidine kinase (TK) promoter in the pTKCAT vector. In addition, the fragment used to create p(−1000)CAT was also cloned into pTKCAT, creating p(−1000)TK. When transfected into U-937 cells, both p(−1000)TK and p(GRR)TK achieved comparably high levels of expression after IFN-$\gamma$ induction (Fig. 5), indicating that the GRR is sufficient to account for IFN-$\gamma$ induction of Fc$_\gamma$RI. When deletions within the GRR insert were made, either from position −35 to −19 or from −57 to −41, all IFN-$\gamma$ induction of expression was lost, suggesting that an intact GRR is necessary for IFN-$\gamma$ induction.

When transfected into HeLa cells, p(GRR)TK expression was induced by IFN-$\gamma$, whereas p(−1000)TK expression was not (Fig. 5). These results further support the supposition that the GRR is necessary and sufficient to confer IFN-$\gamma$ inducibility upon a promoter and that this property can extend to disparate promoters in different cell types. However, the failure of p(−1000)TK to be induced by IFN-$\gamma$ indicates that the context in which the GRR resides can repress this inducibility.

## DISCUSSION

The genomic organization of the huFc$_\gamma$RI gene reflects the high degree of gene duplication that has occurred on chromosome 1 to create the various Fc$_\gamma$Rs (22). Like the genes encoding Fc$_\epsilon$RI$\alpha$ and the other Fc$_\gamma$Rs, the huFc$_\gamma$RI gene encodes each immunoglobulin-like domain on a separate exon and encodes its leader peptide on two exons, with the second being 21 bp in length. The Fc$_\gamma$RI gene is also similar to the genes for Fc$_\gamma$RIII and Fc$_\epsilon$RI$\alpha$ in that it uses a single

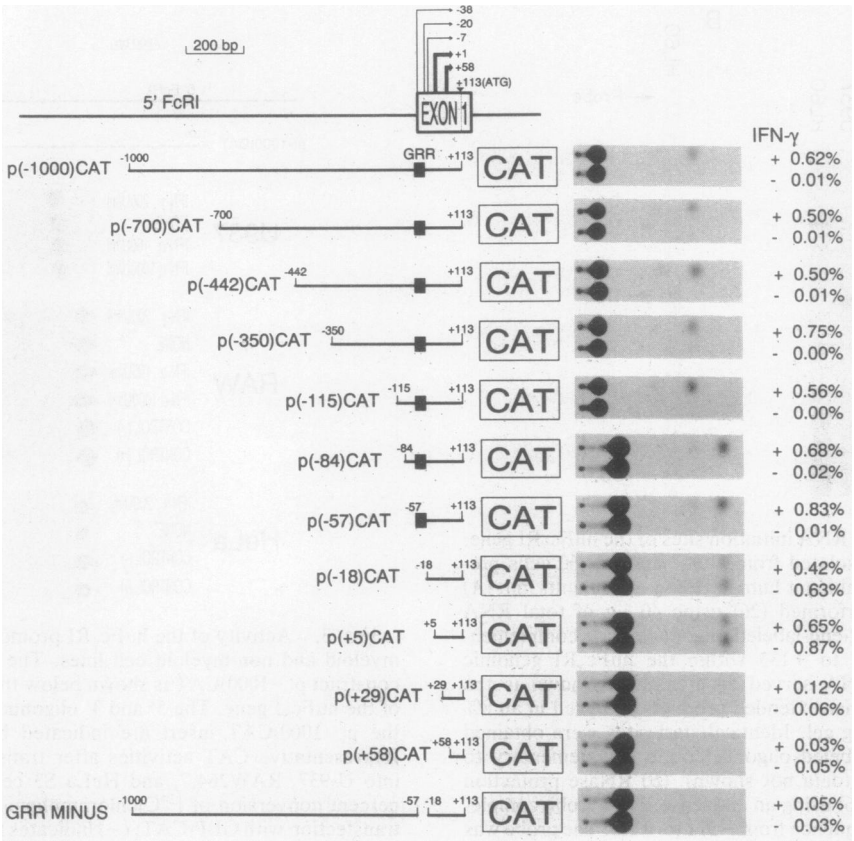


FIG. 4. Deletion analysis of the 5′ end of the Fc$_\gamma$RI promoter. Plasmids with progressive 5′ deletions of p(−1000)CAT were transfected into U-937 cells. Shown are the resultant CAT activities with percent conversion of [$^{14}$C]chloramphenicol. GRR is the 39-bp region from −57 to −18 defined by this analysis. GRR MINUS is p(−1000)CAT from which the GRR has been deleted.

exon to encode its transmembrane and cytoplasmic domains. Three cDNAs have been isolated for huFc$_\gamma$RI (30), two of which demonstrate allelic differences (p135 and p90), while the third (p98/X2) contains divergent 3′ sequence. The genomic sequence reported here is consistent with cDNA p135, with the following exceptions: at what would be cDNA nucleotide 1, a T, rather than a G, was found, and at amino acid 338 an isoleucine (coded by ATT) was found rather than a threonine (coded by ACT). Southern blot analysis of human DNA is consistent with the presence of two highly homologous genes in the genome (34). However, no evidence for a genomic copy of the divergent 3′ sequence has been found, either through screening genomic libraries with this sequence or by PCR amplification of RNA or DNA using this sequence as a primer (data not shown).

Within the promoter of the huFc$_\gamma$RI gene, we find that the 170 bp immediately upstream from the start of translation are sufficient to (*i*) drive transcription of a promoterless reporter gene in macrophage-like cell lines, (*ii*) mediate IFN-γ activation, and (*iii*) confer cell-type specificity. Further, we define the region responsible for IFN-γ induction as the 39 bp at the 5′ end of this 170-bp domain, from −57 to −18. We have shown that deletion of this 39-bp region, the GRR, from the huFc$_\gamma$RI promoter eliminates all induction by IFN-γ, and that a single copy of this GRR can confer strong IFN-γ inducibility to a heterologous reporter in both macrophage and non-macrophage cell lines.

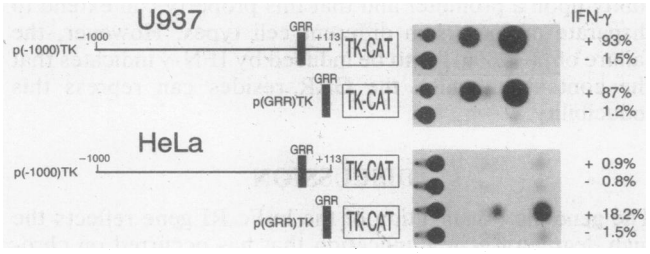


FIG. 5. The GRR is sufficient for IFN-γ induction of a heterologous promoter. Shown are CAT activities and percent conversion after transfection of p(GRR)TK and p(−1000)TK into U-937 and HeLa S3 cells. Conversion of [$^{14}$C]chloramphenicol after transfection of TKCAT into either U-937 or HeLa cells ranged between 1% and 2% and did not change with IFN-γ treatment.

Although the GRR acts as a transcriptional activator in the presence of IFN-γ, it appears to act as a negative regulator in its absence. This is suggested by the high constitutive activity seen after deletion of the GRR by exonuclease III (Fig. 4). This basal activity also implies the existence of a basal promoter for huFc$_\gamma$RI located 3′ to the GRR. Additional negative regulatory elements capable of suppressing this basal promoter appear to reside upstream of the GRR, as elimination of just the GRR from 1.1 kb of huFc$_\gamma$RI promoter does not result in constitutive activity.

The cell-type specificity exhibited by the huFc$_\gamma$RI gene may in part be a property of its basal promoter. This is suggested by the lack of activity in HeLa cells of all exonuclease III-generated mutants. Additional control of cell type-specific expression appears to reside in negative regulatory elements within the Fc$_\gamma$RI promoter, but outside the GRR. Alone, the GRR is not cell type-specific, as it can confer high IFN-γ inducibility upon a heterologous promoter in HeLa cells. However, in the context of 1.1 kb of Fc$_\gamma$RI promoter the GRR is inactive in HeLa cells.

Examination of the GRR reveals the presence of elements thought to confer IFN-γ inducibility upon MHC class II promoters: an X box, an H box, and a γ-IRE (Fig. 6). The role of these elements within MHC class II promoters has been reviewed (17, 18). The X box has been found necessary for

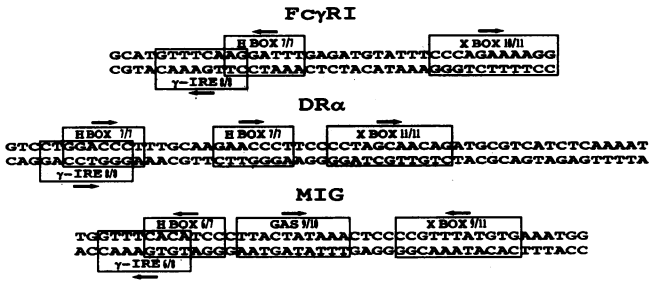


FIG. 6. Sequence comparison of three IFN-γ-responsive genes. Shown are the regions of each promoter known to confer IFN-γ inducibility upon a heterologous promoter. Sequences with homology to elements initially defined for MHC class II promoters (X box, H box, and γ-IRE) or for the GBP gene (GAS) are boxed. The degree of homology with consensus and the orientation of the elements are indicated. [X box, CCYAGMRACNG; H box, RRAYCYK; γ-IRE, CTKKANNY; GAS, TTACTCTAAA (M = A or C; K = G or T).

basal activity and may also play a role in regulating cell-type specificity and IFN-γ induction (17, 20). To confer basal activity upon class II promoters the X box requires the presence, at a conserved distance, of a CAAT-containing sequence known as the Y box (17, 36). The H box has also been called the W box, S box, Z box, or W element. It is located 15–19 bp upstream of the X box in all MHC class II promoters but has been found necessary for IFN-γ induction of only the Eα, DRα, and DQβ genes (17–21). The γ-IRE is a consensus sequence found by sequence comparison of GRRs previously defined for class II promoters (18). As such, it has been proposed as an element necessary for IFN-γ induction of MHC class II genes. For the huFcγRI promoter, we find that the X box, H box, and γ-IRE are all necessary for GRR activity.

The sequences responsible for selective induction by IFN-γ in several other genes have been investigated. The region of the MIG promoter that is responsible for IFN-γ induction (27) contains X, H, and γ-IRE elements (Fig. 6). Similar studies on IP-10 (unpublished work) have found these same sequence elements in regions required for its IFN-γ response. As noted (18), the γ-IRE displays homology to the ISRE, and may represent a sequence motif common to all interferon-responsive genes. Selective induction by IFN-γ might then reflect the influence of sequences, such as X and H boxes, that flank the γ-IRE.

Comparison of the huFcγRI and muFcγRI promoters reveals two regions of homology (Fig. 1C). The first, located at the 3′ end of the GRR, highlights the importance of the X box for IFN-γ induction. The second, located 3′ to the GRR, is homologous to the PU-1 element (37). It is also found in the macrophage-specific muFcγRIII gene (W. Qiu and J.V.R., unpublished observation; A. Ezekowitz, personal communication) and may confer cell-type specificity on the basal promoter.

Analysis of the IFN-α/β-responsive genes has suggested that a common cis-acting sequence (the ISRE) is responsible for the coordinate transcriptional induction of these genes. A similar mechanism may function in the regulation of IFN-γ genes through the GRR.

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