YB-1 DNA-binding Protein Represses Interferon γ Activation of Class II Major Histocompatibility Complex Genes

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Summary

Interferon γ (IFN-γ) is the most potent inducer of class II major histocompatibility complex (MHC) genes. This induction is uniquely mediated by three DNA elements in the promoter region of class II MHC genes. One of these DNA elements, Y, contains an inverted CCAAT box. Previously, we have screened a λgt11 library for Y-binding proteins and identified the YB-1 gene. Here we provide evidence that YB-1 can repress the IFN-γ induction of class II MHC promoter as well as the Invariant chain (Ii) gene which also contains a Y element in its promoter. This was demonstrated by cotransfecting a YB-1 expression vector with promoter-reporter gene constructs. As an alternate approach, an efficient transient transfection system was developed which resulted in a >70% transfection efficiency. Transfection of YB-1 by this procedure resulted in the near abrogation of IFN-γ induced HLA-DR antigen and mRNA expression. These findings show the functional suppression of class II MHC gene induction by the YB-1 protein.

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lass II MHC gene products play a variety of important roles in immune regulation (reviewed in 1-3). These molecules control the acquisition of the mature T cell repertoire and serve as restriction elements for CD4+ T cells. These functions place the regulation of class II MHC antigens as an important topic in immune regulation. The expression of class II MHC genes is primarily regulated at the level of transcription. In the past few years, we and others have delineated an array of cis-acting elements important for optimal class II gene regulation and have identified proteins that bind to these elements. The cis-acting regulatory elements of the DRA gene are probably the best analyzed, and include three elements (S, X, and Y) that are also found in other class II MHC promoters (4-7). The X and Y elements constitute the conserved class II box present in the upstream region of all class II MHC promoters studied to date (8, 9).

These two elements are separated by a 19–21-bp spacing that is conserved in length but not in sequence. The Y element contains an inverted CCAAT element, and the X element has been functionally divided into two subregions, X1 and X2, based on the separate interactions of these subregions with the RF-X and hXBP-1 recombinant DNA-binding proteins, respectively (10, 11). The S sequence (also known as H, or W/Z which is a larger DNA sequence) is a heptamer sequence located upstream of the class II box (12-17). These three elements are important for basal gene transcription, and thus far, they are inseparable from elements required for the IFN-γ induction of class II MHC genes (12-19).

The YB-1 DNA-binding protein was initially identified by using radiolabeled Y element sequence to screen a λgt11 expression cDNA library (20). The recombinant YB-1 protein exhibits specificity for the Y element because mutations of an inverted CCAAT sequence in the Y element can abrogate its ability to interact with YB-1. An intriguing feature is the inverse relationship between levels of YB-1 and DRA in IFN-γ-activated cell lines. Consequently, we suggested a model wherein YB-1 negatively regulates class II MHC gene expression (20). The findings reported here provide strong evidence to support this model.

Materials and Methods

Plasmids. pSFFV-YB-1 and the control pSFFV-neo expression plasmids (19) are depicted in Fig. 1 A. DRA-chloramphenicol acetyl transferase (CAT)1 constructs and the control plasmid (CAT-SK+) that lacks DRA sequence have been described in detail previously.

1 Abbreviations used in this paper: CAT, chloramphenicol acetyl transferase; Ii, invariant chain gene; β-gal, β-galactosidase; SFFV, spleen focus forming virus.
Suppression of IFN-γ Class II MHC Gene Activation

Results

YB-1 Suppresses Class II MHC Promoter Activity. The effect of YB-1 protein on IFN-γ-activated DRA promoter function was assayed by introducing an expression vector containing the YB-1 cDNA into an IFN-γ-responsive, human glioblastoma line U373-MG. This line was chosen because our previous analysis and delineation of the class II MHC promoter were performed with this line. In addition, IFN-γ-induced class II MHC gene expression in this line is high (22), better permitting the detection of any suppressive effects of YB-1.

The YB-1 cDNA was subcloned into an expression vector driven by the SFFV long terminal repeat (24). The resulting plasmid is shown in Fig. 1A. SFFV-YB-1 was cotransfected with a DRA-CAT construct, 5'Δ-152, (Fig. 1B) (20). As a negative control, 5'Δ-152 was also cotransfected with SFFV-neo which lacks the YB-1 sequence. 5'Δ-152 was inducible by IFN-γ as shown previously (Fig. 1C, lanes 1 and 2). The effect of IFN-γ is mediated through the DRA promoter sequence because removal or mutation of these sequences in the parental plasmid, pSFFV-neo, had little effect on either the basal or stimulated CAT expression, although there was only a small effect on basal expression (Fig. 1C, lanes 3 and 4). In the control vector, pSFFV-neo, had little effect on either the basal expression or IFN-γ-induced expression of 5'Δ-152 DRA-CAT. In striking contrast, the cotransfection of pSFFV-YB-1 with 5'Δ-152 resulted in a substantial decrease of IFN-γ-induced CAT expression, although there was only a small effect on basal expression (Fig. 1C, lanes 5, 6, 9, and 10). Cotransfection of the control vector, pSFFV-neo, had little effect on either the basal expression or IFN-γ-induced expression of 5'Δ-152 DRA-CAT. In striking contrast, the cotransfection of pSFFV-YB-1 with 5'Δ-152 resulted in a substantial decrease of IFN-γ-induced CAT expression, although there was only a small effect on basal expression (Fig. 1C, lanes 5, 6, 9, and 10).

Figure 1. YB-1 protein suppresses IFN-γ induction of a DRA-CAT reporter construct. (A) The construction of pSFFV-YB-1 was achieved by cloning YB-1 in an expression vector pSFFV-neo (9). (B) A depiction of the reporter construct 5'Δ-152 DRA-CAT (20). (C) The trans-activation of 5'Δ-152 by pSFFV-YB-1: YB-1 expression vector (designated Y) or control vector pSFFV-neo (designated C) was cotransfected with 5'Δ-152, Y-MUT1 (a mutant of 5'Δ-152 with a mutated Y box, [19]), or CAT-SK + (the parent plasmid without the DRA sequence, [19]). Transfection was performed as described previously in the presence (+) or absence (−) of 400 U/ml IFN-γ (19).
Table 1. YB-1 Protein Suppresses the IFN-γ Induction of DRA, DQB and li Promoters

| Experiment no. | Promoter | Reporter construct | trans-acting construct | Percent acetylation ± interferon | Fold induction by interferon<sup>1</sup> | Percent inhibition by YB-1 |
|---------------|----------|--------------------|-------------------------|---------------------------------|-----------------------------------|-----------------------------|
| 1             | DRA      | 5′A-152            | pSFFV-YB-1              | 5.88/0.33                       | 16.9X                             | 74                          |
|               |          |                    | pSFFV-neo              | 36.30/0.55                      | 66.0X                             |                             |
| 2             |          |                    | pSFFV-YB-1              | 2.03/0.30                       | 6.8X                              | 66                          |
| 3             |          |                    | pSFFV-neo              | 7.03/0.35                       | 20.1X                             |                             |
| 4             |          |                    | pSFFV-YB-1              | 3.74/0.25                       | 15.0X                             | 56                          |
|               |          |                    | pSFFV-neo              | 13.00/0.38                      | 34.2X                             |                             |
| 1             | DQB      | DQB2500CAT         | pSFFV-YB-1              | 1.75/0.25                       | 7.0X                              | 85                          |
|               |          |                    | pSFFV-neo              | 25.00/0.52                      | 48.1X                             |                             |
| 2             | li       | 790-In CAT         | pSFFV-YB-1              | 4.47/0.80                       | 5.6X                              | 70                          |
| 3             |          |                    | pSFFV-neo              | 19.00/1.00                      | 19.0X                             |                             |
| 2             |          |                    | pSFFV-YB-1              | 17.00/1.00                      | 17.0X                             | 59                          |
| 3             |          |                    | pSFFV-neo              | 41.00/1.00                      | 41.0X                             |                             |
| 1             | li       | 790-In CAT         | pSFFV-YB-1              | 39.00/2.00                      | 19.5X                             | 37                          |
| 2             |          |                    | pSFFV-neo              | 62.00/2.00                      | 31.0X                             |                             |
| 2             | li       | 790-In CAT         | pSFFV-YB-1              | 12.00/2.00                      | 6.0X                              | 59                          |
|               |          |                    | pSFFV-neo              | 29.00/2.00                      | 14.5X                             |                             |
| 1             | HSP70    | -77HSP70CAT        | pSFFV-YB-1              | 1.07/0.14                       | 0.9X                              | 18                          |
| 2             |          |                    | pSFFV-neo              | 1.11/1.00                       | 1.1X                              |                             |
| 1             | HTK      | HTK-CAT            | pSFFV-YB-1              | 1.07/0.62                       | 1.7X                              | NI*                         |
| 2             |          |                    | pSFFV-neo              | 0.98/1.00                       | 1.0X                              |                             |
| 1             | li       | 790-In CAT         | pSFFV-YB-1              | 0.84/0.87                       | 1.0X                              | NI                          |
| 2             | li       | 790-In CAT         | pSFFV-neo              | 0.85/1.00                       | 0.9X                              | NI                          |

The experiments were performed as described in the legend to Fig. 1.

<sup>*</sup> No inhibition.

<sup>1</sup> Percent CAT-mediated acetylation in the presence of IFN-γ/Percent acetylation with IFN-γ.

To determine if YB-1 could suppress other class II MHC promoters, the effect of YB-1 on IFN-γ-induced DQB promoter activity was similarly tested by cotransfecting pSFFV-YB-1 with DQB2500CAT (12). DQB2500CAT promoter contains the S, X, and Y elements that are necessary for IFN-γ induction. As shown in Table 1, pSFFV-YB-1 suppressed the IFN-γ induction of DQB2500CAT by an average of 65% in two experiments, but had little effect on the basal expression of this plasmid. Furthermore, the effect of YB-1 on the li chain promoter was also tested. The li chain plays an important role in the presentation of specific antigens due to its ability to target class II MHC antigens to appropriate cellular compartments (25-27). The expression of li is coregulated with the class II MHC genes (28, 29). Interestingly, the li promoter contains S, X, and Y homologues that mediate both basal and IFN-γ inducibility (21, 30-32). pSFFV-YB-1 also suppressed the IFN-γ inducibility of a construct (790-InCAT) that contains the li chain promoter linked to a CAT reporter gene.

To ascertain if the suppressive effects of YB-1 are specific to these promoters, and not due to a general downregulation of transcription, the effects of pSFFV-YB-1 on two other unrelated promoters were tested (Table 1). This was tested as described above by cotransfecting pSFFV-YB-1 with a promoter-driven CAT construct. As shown in Table 1, neither pSFFV-neo nor pSFFV-YB-1 affected CAT expression of HTK-CAT or the -77HSP70CAT. This was true regardless of the presence of IFN-γ.

Development of a High Efficiency Transfection System. To address the possibility that the usage of a reporter gene system may not reflect the state of the endogenous gene, the suppressive effect of YB-1 on endogenous class II MHC gene expression was assessed. These experiments were made possible by the development of a high efficiency transfection...
system. The efficiency of this system was revealed by the percentage of cells that express the β-gal enzyme after transfection with a pSVβ-Gal construct. β-gal positive cells were scored by the conversion of a nonfluorescent substrate to a fluorescent enzyme product that was quantitated by FACS®. As shown in Fig. 2, transfection of U937 with 20 μg of pSV β-gal resulted in a complete shift of the curve, and >70% of the cells expressed β-gal at a level significantly above background.

Figure 2. Transfection of U937 results in high-efficiency β-gal gene expression. U937 cells were transfected with pSV β-gal as described in Materials and Methods. The expression of β-gal was assayed by the conversion of fluorescein di-β-galactopyranoside to a fluorescent enzymatic product which was measured by FACS®. (Dotted line) mock transfected cells. (Solid line) cells transfected with 20 μg pSV β-gal.

YB-1 Suppresses IFN-γ–induced MHC Class II mRNA and Protein Expression. Using this protocol, the effect of YB-1 on DRB was assessed. In these experiments, pSFFV-YB-1 was transiently transfected into U937 (20), an IFN-γ–responsive human macrophage cell line. These cells were incubated in the absence of IFN-γ, and the RNA was isolated and assayed for DRB transcript expression by Northern hybridization analysis. In addition, surface HLA-DR antigen expression on cells from the same experiment was assayed by FACS®. As shown in Fig. 3A, Northern hybridization shows that IFN-γ enhanced DRB-specific mRNA in U937 as expected. In contrast, the transfection of pSFFV-YB-1 into U937 greatly diminished the level of DRB mRNA that was induced by IFN-γ, although the negative control plasmid pSFFV-neo did not produce such an effect. The difference in DRB mRNA levels is not due to variations in the quantity of RNA in these samples, because the hybridization signals produced by an actin cDNA probe are similar among these samples (Fig. 3B). Parallel FACS® analysis revealed that the transfection of pSFFV-YB-1 into U937 also greatly reduced IFN-γ–induced HLA-DR surface antigen expression. Transfection with the negative control pSFFV-neo had little effect (Fig. 4). Likewise, YB-1 did not affect the staining pattern with a negative control antibody (ASA11) significantly. These results have been reproduced 19 times out of 23. Taken together, these results show that YB-1 can suppress IFN-γ–induced endogenous class II gene expression.

Discussion

The ability of YB-1 to suppress IFN-γ–induced class II MHC and Ii chain gene expression has broad implications in immune regulation. IFN-γ represents a potentiator of the immune response via its ability to upregulate a number of genes important in immune reactivity, most notably the class
body. FL1 represents fluorescence intensity expressed as an arbitrary unit.

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