The Small RNA Gene Activator Protein, Sp1 Postoctamer Homology-binding Factor/Selenocysteine tRNA Gene Transcription Activating Factor, Stimulates Transcription of the Human Interferon Regulatory Factor-3 Gene*

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Many small nuclear RNA gene promoters are activated by Sp1 postoctamer homology (SPH)-binding factors/selenocysteine tRNA gene transcription activating factor (SBF/Staf). Whereas this transcription factor was initially identified by its ability to bind to SPH elements in such promoters, it was more recently shown to have the capacity to activate transcription of a synthetic mRNA gene promoter through a distinct activation domain. Here, we show that the human interferon regulatory factor-3 (IRF-3) gene promoter contains a functional SPH element that is bound by SBF/Staf in vitro and in transfected cells.

Eukaryotic transcriptional activator proteins are usually multifunctional. For example, activator proteins that bind a specific DNA sequence are organized in a modular fashion, with a DNA-binding domain (DBD)1 and one or more activation domains (1). In addition, activator proteins are likely to be used in the transcription of more than one gene, each of which contains a similar DNA-binding site in the promoter or enhancer. Furthermore, a single activation domain can target multiple general transcription factors or coactivator complexes while effecting transcriptional stimulation (2, 3).

Small nuclear RNA (snRNA)-type promoters appear to be relatively simple models in which to investigate transcriptional activation (recently reviewed in Ref. 4). SnRNA genes are transcribed by either RNA polymerase II (pol II) (e.g. U1 and U2) or RNA polymerase III (pol III) (e.g. U6) (5, 6). In addition, a number of other small RNA genes, such as those encoding 7SK, MRP, and selenocysteine tRNA, contain snRNA-type pol III promoters (7–9). All vertebrate snRNA-type promoters are or-
SBF/Staf Regulates IRF-3 Gene Transcription

Medical School (30). The IRF-3 5′-flanking region between −206 and −129 was amplified by PCR and subcloned into pCR2.1-TOPO (Invitrogen) to construct pCR2/IRF3. Isolates were recovered that contained the IRF-3 insert in both orientations within the plasmid. To construct pGEM/IRF3FOR/Dl-84/U6/CFREEM and pGEM/IRF3REV/Dl-84/U6/CFREE, pGEM/IRF3FOR/Dl-84/U6/CFREE was dephosphorylated with calf intestinal alkaline phosphatase and self-ligated. Transfections, Primer Extension, and Luciferase Assays—Human 293 cells were transfected in 100-mm dishes with 10 μl of U6/CFREE reporter plasmid plus 10 μg of pGEM/Cβ3 using the calcium phosphate method, and total RNA was isolated and analyzed by primer extension as described previously, except that a longer primer was used to detect SBF/Staf. Isolates were recovered that contained the lacZ coding region in both orientations. Insertion frequencies of the selected fragments were quantitated using a STORM PhosphorImager (Molecular Dynamics). Transfection experiments shown in Fig. 4 used 60-mm dishes of human 293 cells containing 1.0 × 10^6 cells seeded 24 h prior to transfection. One μg of pIRF3 reporter DNA and 0.5 μg of pSV-βgal (Promega) were introduced using FuGENE 6 reagent (Roche Molecular Biochemicals) following the manufacturer’s protocol. After 48 h, cells were harvested by scraping, washed with phosphate-buffered saline, and total lysates prepared in 0.1 M potassium phosphate (pH 7.8), 0.2% Triton X-100. Luciferase and β-galactosidase activities (GALACTO/Light Plus assay system) of cells lysates were measured by a microplate luminometer (Packard Luminco). Transfection experiments shown in Fig. 5 used 24-well microwell plates containing 1.0 × 10^5 human 293 cells per well seeded 24 h prior to transfection. Using the calcium phosphate protocol, each sample was transfected with 10 ng of pIRF3 reporter plasmid, 50 ng of pSV-βgal, and 1 ng of pGEM/IRF3-SBF expression plasmid. Cells were harvested after 36 h, and lysates assayed for luciferase and β-galactosidase.

Fig. 1. Presence of SBF and OCT elements in human IRF-3 gene promoter region. DNA sequences in the human IRF-3 and U6 snRNA gene 5′-flanking regions are compared with a consensus SBF element determined by binding site selection with the Xenopus Staf protein (37). The upper case type for the SBF consensus represents nucleotide bases that were present in >70% of the selected fragments, whereas the positions shown in lower case were selected at lower frequencies. The underlined sequence highlights a consensus octamer motif. The nucleotide at position −155 of the IRF-3 promoter (denoted in bold) was reported as a T in the original sequence (30), but is a G in all plasmid constructs used in this work.

Identification of SBF and OCT Elements in Human IRF-3 Gene Promoter—The 5′-flanking sequence of the human IRF-3 gene contains a putative SBF element centered at position −163 and a consensus octamer motif centered at position −181 (Fig. 1). Close linkage of OCT and SBF motifs is a hallmark of the enhancer-like regions of many vertebrate snRNA gene promoters, whether they are transcribed by RNA polymerase II or III (16, 17). The presence of snRNA gene SBF elements in mRNA gene promoters has been described recently in only a single example, the mouse cytosolic chaperonin containing t-core complex subunit a gene (29). To examine whether the IRF-3 SBF and OCT sites could be bound by factors in vitro, electrophoretic mobility gel shift, and DNase I footprinting assays were performed using a radiolabeled DNA fragment containing the sequence from −206 to −129. Several complexes were formed on the IRF-3 fragment using a HeLa cell S100 extract (Fig. 2A). The major complexes were composed of octamer-binding factor, presumably Oct-1, and SBF/Staf, since they were specifically competed by the addition of excess unlabeled consensus octamer oligonucleotide (Fig. 2A, lanes 2–4) or human U6 SBF oligonucleotide (Fig. 2A, lanes 5–7). Recombinant SBF/Staf expressed in Escherichia coli bound the same IRF-3 promoter fragment, and binding specificity was demonstrated by competition with U6 SBF, but not OCT, oligonucleotide (Fig. 2B). Furthermore, sequence-specific binding to the IRF-3 gene promoter by either recombinant Staf or bacterial recombinant SBF/Staf (Fig. 2C) was protected in the footprint (Fig. 2C, lanes 4 and 5), similar to the footprint of recombinant SBF/Staf on the human U6 SBF element (27). This lack of protection may reflect the poor fit of the 3′-end of the IRF-3 SBF element to the consensus (Fig. 1), and is consistent with the documented flexibility of DNA binding by Staf zinc fingers, notably zinc finger 1 (37).
SBF/Staf Regulates IRF-3 Gene Transcription

Enhancer Activity of the IRF-3 SPH + OCT Region for the Human U6 Promoter—After demonstrating that the IRF-3 SPH and OCT sites were potential targets for factor binding in vitro, their capacity for transcriptional activation was tested. Initially, the IRF-3 SPH + OCT segment (−206/−129) was fused to the basal human U6 snRNA gene promoter (dl-84/U6/CFREE) in both orientations, and tested for activity in transfected human 293 cells. In either orientation the IRF-3 SPH + OCT segment stimulated snRNA promoter transcription approximately 6–9-fold (Fig. 3, lanes 2 and 3). This stimulatory activity was comparable to that exerted by the U6 SPH motif (Fig. 3, lane 4), but −20% of that provided by the U6 SPH + OCT distal region (Fig. 3, lane 5). Previously we have shown that the U6 SPH and OCT elements were approximately equally effective in such a transfection assay, and their combination was only slightly greater than additive (23).

The SPH Element Is Functional in the IRF-3 Promoter—Next, the roles of the SPH and OCT elements were tested in the IRF-3 promoter. Clustered point mutations were introduced to disrupt each element separately (SPHMUT or OCTMUT), and together in the same promoter (SPHMUT/OCTMUT). IRF-3 molar excess, respectively, of consensus octamer motif from the human U6 distal region (OCTCON); lanes 5–7, 30-, 300-, and 3000-fold molar excess, respectively, of human U6 SPH motif. B, binding of recombinant human SBF-(76–626), expressed by in vitro transcription/translation, was analyzed by electrophoretic mobility shift assay. Approximately 3 fmol of radiolabeled IRF-3 (−206/−129) DNA probe were mixed with translation extract programmed with pET/hSBF-(76–626) DNA in the absence of competitor DNA (lane 2), or with unlabeled consensus OCT double-stranded oligonucleotide (30- and 300-fold molar excess in lanes 3 and 4, respectively), or with unlabeled U6 SPH double-stranded oligonucleotide (30- and 300-fold molar excess in lanes 3 and 6, respectively). C, binding of IRF-3 (−206/−129) radiolabeled DNA by recombinant hSBF-(76–626) or Oct-1 POU domain detected by DNase I footprinting. Lanes 1 and 2 show protection by ~40 and 100 ng, respectively, of Oct-1 POU domain protein, and lanes 3–5 show protection after addition of ~10, 50, and 100 ng, respectively, of hSBF-(76–626) protein. The sample electrophoresed in lane 6 contained no added transcription factor prior to DNase I treatment.

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Fig. 3. The IRF-3 (SPH + OCT) region can act as a U6 promoter enhancer element in transfected cells. Human 293 cells were transfected by the calcium phosphate technique with plasmid DNAs containing the basal human U6 promoter (dl-84) or various constructs in which the IRF-3 (SPH + OCT) region (IRF3FORW or IRF3REV), or human U6 SPH or U6 (SPH + OCT) elements were ligated to the basal promoter. Expression from exogenous promoters was detected by primer extension. “CFREE” represents transcription from the U6 promoter, and “cβ3” represents transcription from a co-transfected chicken β-tubulin plasmid used as a control to normalize for variable transcription efficiency. The fold-activation noted at the bottom was determined after quantitation of band intensities by phosphorimaging. After background subtraction, the CFREE/cβ3 ratio was calculated and compared with the value from the dl-84 (basal) promoter (lane 1).
promoter activities were determined by quantitation of luciferase reporter gene levels in transfected human 293 cells. Disruption of the SPH element resulted in a decrease of promoter activity to ~25% of wt (Fig. 4, SPHMUT). In contrast, mutation of OCT caused a small, but reproducible increase in activity (Fig. 4, OCTMUT). When both elements were mutated, IRF-3 promoter activity was reduced to the same extent as for the SPHMUT construct. The data shown in Fig. 4 are from transfection experiments using 1 µg of luciferase reporter plasmid (in 60-mm dishes), but similar results were obtained when either 0.5 or 2 µg of reporter plasmid were employed (data not shown). Furthermore, IRF-3/SPHMUT promoter activity was similarly reduced to ~25% of wt in transfected HeLa cells (data not shown).

**Binding of SBF/Staf to the IRF-3 Promoter in Transfected Cells**—Reduced transcription from the SPHMUT promoter demonstrated the importance of the DNA sequence from −170 to −161, but did not prove a role for SBF/Staf in the IRF-3 promoter in vivo. In order to examine the activation of this promoter by SBF/Staf, cells were co-transfected with expression plasmids encoding GAL4 DBD/SBF fusion proteins and an IRF-3 promoter/luciferase reporter plasmid containing a GAL4-binding site. The SPHMUT/IRF-3 reporter plasmid had been designed to convert the SPH element to a GAL4 element. Two GAL4 DBD/SBF fusion plasmids were constructed. One, pCI/GAL4/SBF-(1–140), contained the amino-terminal sequence of SBF/Staf, which includes 4 imperfect 15-amino-acid repeats previously shown to activate synthetic thymidine kinase reporter gene in injected Xenopus oocytes or transfected Drosophila cells (28). A second fusion protein, expressed from pCI/GAL4/SBF-(136–223), contained a region of SBF/Staf reported to activate snRNA gene promoters (28).2 Expression of GAL4/SBF-(1–140) stimulated transcription from the SPHMUT/IRF-3 promoter 2-fold, whereas the GAL4/SBF-(136–223) fusion protein had no effect (Fig. 5). Furthermore, expression of the GAL4 DBD-(1–94) alone did not significantly stimulate expression from the SPHMUT promoter (results not shown). In these experiments the effect of the SPH mutation was somewhat more severe than shown previously (13% of wt in Fig. 5 versus 27% of wt in Fig. 4), possibly because smaller numbers of cells and plasmid DNAs were used for the transfection assays. Both GAL4 fusion proteins and the GAL4 DBD protein were expressed at similar levels in transfected 293 cells as determined on Western blots using antibody directed against the GAL4 DBD (data not shown). The GAL4/SBF-(1–140) fusion protein was unable to reconstitute full, wt IRF-3 activity to the SPHMUT promoter, but the stimulatory activity was significant compared with the control GAL4/SBF-(136–223) and GAL4 DBD proteins.

To further investigate the binding of SBF/Staf to the IRF-3 promoter, chromatin immunoprecipitation was employed with

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2 G. R. Kunkel, unpublished results.
radiolabeled PCR products on a 20% gel. The antibody-selected DNA samples were determined by electrophoresis of 5% of the amount of immunoselected sample assayed by PCR. Lower amounts of immunoselected sample were seen for DNA containing no added DNA, and “total” lanes (supplementary data not shown). Sheared chromatin from formaldehyde-treated cells was immunoselected with anti-SBF antibodies (lanes 2 and 5) or preimmune antibodies (lanes 3 and 6), and DNA was purified following reversal of cross-links. The relative amounts of IRF-3 promoter sequence in the unselected or antibody-selected DNA samples were determined by electrophoresis of radiolabeled PCR products on a 20% gel. The “total” lanes (1 and 4) show PCR of approximately double the amount of sample used for antibody selection. B, binding of SBF/Staf to the endogenous human U6-1 gene was investigated by chromatin immunoprecipitation using primer sets to amplify either the near upstream region (−307 to −90), encompassing the SPH element (lanes 2–5), or a far upstream region (−1880 to −1760) as a control (lanes 7–10). Lanes marked “Buffer” contained no added DNA, and “5% Total” contained unselected DNA at 5% of the amount of immunoselected sample assayed by PCR.

SBF/Staf regulates IRF-3 gene transcription

In this report, we demonstrate that the transcriptional activator, SBF/Staf, first characterized for its role at snRNA gene promoters, is an important stimulatory factor for the human IRF-3 gene promoter. The SPH element at −160 is bound by recombinant SBF/Staf or the endogenous protein in HeLa cell extracts (Fig. 2). Disruption of the SPH element causes decreased promoter activity that is partially restored by co-expression of the SBF/Staf mRNA activation domain which is directed to the mutant promoter (Fig. 5). Furthermore, chromatin immunoprecipitation results show that SBF/Staf binds to the wt IRF-3 promoter in transfected cells (Fig. 6).

The potential for SBF/Staf activation at mRNA gene promoters was demonstrated first using a synthetic tk/CAT promoter containing multiple activator-binding sites (28). With this report, at least two bona fide mammalian mRNA promoters have been shown to contain functional SPH elements that are binding sites for this activator. Recently, the mouse chaperonin containing t-complex polypeptide 1 α-subunit gene promoter was found to contain two SPH elements at positions −70 and −20 (29). At present, the limited dataset of mRNA promoters containing SPH elements makes it impossible to determine whether correlations exist between other features of these promoters. Whereas the mouse chaperonin containing t-complex polypeptide 1 α-subunit promoter is apparently TATA-less, the tk promoter contains a documented TATA box (38). The human IRF-3 promoter does not contain a canonical TATA box at the normal location, but it is not known whether a functional TATA element is present (30). Both the aforementioned synthetic tk/CAT promoter and mouse chaperonin containing t-complex polypeptide 1 α-subunit promoter contain multiple SBF/Staf-binding sites. We found only one SPH site in the −206/−129 region of the human IRF-3 promoter, but cannot rule out the possibility of other sites outside this region. However, our chromatin immunoprecipitation results with the SPH promoter do not indicate any strong SBF/Staf-binding sites in a more proximal location of this promoter.

It is not known what other transcription factors operate at the human IRF-3 promoter. We noticed a consensus octamer motif just upstream of the SPH motif at a position of approximately −180 (Fig. 1), and showed that this site was bound by Oct protein or recombinant Oct-1 POU domain in vitro (Fig. 2, A and C). However, in contrast to the SPH promoter mutation, disruption of the octamer motif (OCTMUT) resulted in only a minimal effect on the IRF-3 promoter (Fig. 4). In fact, expression from the OCTMUT promoter was reproducibly higher, suggesting that a negative regulatory element was disrupted. Presently, it is not known whether Oct protein binds to this site in vivo, although this could be examined using chromatin immunoprecipitation. Indeed, a possible USF site overlaps the IRF-3 promoter, but cannot rule out the possibility of other sites outside this region. However, our chromatin immunoprecipitation results with the SPH promoter do not indicate any strong SBF/Staf-binding sites in a more proximal location of this promoter.

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but none have been verified experimentally (30).

A previous report did not identify a difference in IRF-3 promoter activity when the region containing the SPH element (−195 to −127) was deleted (30). It is not clear why our results are apparently in contradiction. However, it is possible that this region contains both positive (e.g. SPH) and negative regulatory elements that counteract each other. Alternatively, the previous investigators used a different cell line for their transfection experiments (2FTGH cells), that could express a different repertoire of factors that bind to the IRF-3 promoter. We found similar results with both human 293 and HeLa cells.

In co-transfection experiments, expression of a GAL4 DBD/SBF-(1–140) fusion protein partially restored IRF-3 promoter activity to the SPHMUT template that contained a single GAL4-binding site (Fig. 5). However, even when larger amounts of this expression plasmid were added, wt promoter activity was not attained (results not shown). Possibly, to regain wt activity, multiple GAL4-binding sites would be necessary in this synthetic system. Alternatively, a larger segment of SBF/Staf containing multiple activation domains might be necessary for efficient IRF-3 promoter transcription complex assembly. Nevertheless, our results indicate that the amino-terminal portion of SBF/Staf, containing the 15-amino acid repeats, can function as an activation domain for the IRF-3 gene promoter, and corroborate previous results using Xenopus Staf and the synthetic tk/CAT promoter (28). Future work will delineate the mechanisms by which SBF/Staf uses two separate domains to activate mRNA versus snRNA gene promoters.

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