Multiprotein complexes present at the MIF motifs flanking the promoter of the human *c-myc* gene

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Abstract The activated *c-myc* allele in Burkitt's lymphoma is associated with a clustering of somatic mutations within a discrete domain of intron I that define protein recognition sequences, designated as myc intron factors (MIF-1, MIF-2 and MIF-3). We have previously shown that MIF-1 binding activity consists of two polypeptides, myc intron binding polypeptide (MIBP1) and RFX1. In the present study we identified two polypeptides, p105 and p115, and showed that these proteins give rise to a DNA–protein complex at the MIF-2 as well as the adjacent MIF-1 site. In addition, we demonstrated that all four proteins interact with a novel MIF-1 like motif upstream from the *c-myc* promoter region, designated 5′MIF. These data suggest a model, where the interactions of MIBP1/RFX1 and p105/p115 with the MIF-like sites may play a role in the promoter topology of the *c-myc* gene.

Key words: Transcription; *c-myc*; Intron; myc intron binding polypeptide; RFX1

1. Introduction

The expression of the protooncogene *c-myc* is linked with cell proliferation, differentiation and the development of human tumors. The regulation of *c-myc* gene expression is controlled by several protein factors and their *cis* elements that have been identified in the 5′ upstream and untranslated exon I regions of the *c-myc* gene [1–3]. In addition, several discrete protein binding sites have been identified within intron I near the boundary of exon I designated myc intron factors (MIF-1, MIF-2 and MIF-3) [4,5]. MIF-1 was shown to bind a nuclear phosphoprotein and it was demonstrated that protein binding was abolished by a point mutation present in the corresponding region of a Burkitt's lymphoma *c-myc* DNA [4,6]. Characterization of the MIF-1 binding site indicated that MIF-1 activity consisted of two polypeptides, the myc intron binding polypeptide (MIBP1) and the major histocompatibility (MHC) class II promoter-binding protein RFX1 [7]. RFX1 was initially identified as a protein that binds to the X-box sequence in the promoter of the MHC class II gene and subsequently shown to function as a transactivator of the hepatitis B virus (HBV) enhancer through its interaction with the EP binding element [8–10]. In addition, RFX1 was shown to regulate several other mammalian genes, including the human leukemia (PCNA) promoter and the interleukin 5 receptor α promoter [11,12]. The RFX-type transcription factor Daf-19 was recently shown to regulate sensory neuron cilium formation in *Caenorhabditis elegans* [13]. It has been previously shown that RFX1 associates in vivo with MIBP1 and that this heterodimer is present, by gel shift analysis, in the slower migrating 'A' complex at the *c-myc* (MIF-1) site, at the MHC class II (X-box) RFX binding site, [7,9] and at the regulatory regions of several viral genes, including HBV, Epstein Barr virus, cytomegalovirus and polyoma virus [7,10,14,15]. It was also shown recently that protein levels and DNA binding activity of RFX1 and MIBP1 are induced during granulocytic differentiation of HL60 cells, which correlated with a decrease in *c-myc* levels in these cells in vivo [16].

There are two additional DNA–protein complexes that have been observed by gel shift analysis to form at the *c-myc* (MIF-1) site designated components 'B' and 'C' [7,15]. DNA–protein complexes 'A' and 'B' are present at the *c-myc* (MIF-1), MHC class II (RFX), HBV (EP) and other viral sites, while 'complex C' is unique to the MIF-1 and the adjacent MIF-2 binding sequences and has not been detected at the RFX and the EP recognition sites [7,15]. In this study we identified two polypeptides, p105 and p115 that give rise to 'complex C' at the MIF-1 and MIF-2 recognition sites. In addition, we showed that all four proteins, MIBP1/RFX1 and p105/p115, interact with a novel MIF like motif 600 base pair upstream from the *c-myc* promoter region, designated as 5′MIF. We also showed that MIF-1 [7,15] and MIF-2 but not the 5′MIF recognition sequence can regulate heterologous promoter activity in vivo. These data suggest a model, where the interaction of MIBP1/RFX1 and p105/p115 with three MIF-like sites may play a role in the promoter topology of the *c-myc* gene.

2. Materials and methods

2.1. Plasmids and oligonucleotide probes

Double-stranded oligonucleotides were synthesized as follows: MIF-1, GATCTAGAGTAGTTATGGTAACTGGG; MIF-2, GATCACCTTATGAATATATTCACACA; 5′MIF, GATCCGCGTTGCTGGGTTATTTTAATCA. The double stranded oligonucleotides were multimerized and fragments containing five tandem copies were gel-purified and cloned into the *Bgl*II site of the pCAT-P vector (Promega) as described previously [7]. All plasmids were confirmed by sequencing. The pGL2-P luciferase vector (Promega) was used to correct for transfection efficiency.

2.2. Cell culture and DNA transfections

HeLa cells were obtained from the American Type Culture Collec-

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tion (ATCC). The cells were grown in Dulbecco's modified Eagle's medium (DMEM) (Biofluids) with 10% fetal calf serum and 50 mg each of streptomycin and penicillin per ml. For each transfection, 2.0×10^6 cells were plated in 100 mm dishes and incubated overnight at 37°C. Cells were transfected by calcium phosphate precipitation for 5 h using either 5 mg of pCAT-P or pCAT-P containing an insert consisting of one to five copies of the indicated DNA binding site. 1 μg of pGL2-Luc was cotransfected to control for transfection efficiency. At 42 h the dishes were washed with cold phosphate buffered saline (PBS), scraped and the cell pellets were resuspended in 100 μl of 100 mM KH_2PO_4 pH 7.8 with 1 mM DTT and stored at −20°C. CAT and luciferase assays were performed as described previously [5,17].

2.3. Preparation of nuclear and whole-cell extracts

Nuclear extracts were prepared according to the modified method of Schreiber [18]. Pelleted cells were resuspended in buffer A (10 mM hydroxyethyl-piperazine *N*-2′-ethanesulfonic acid (HEPES) pH 7.5, 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 0.5 mM dithiothreitol (DTT) and 0.5 mM phenylmethylsulfonyl fluoride (PMSF)) and Nonidet p-40 (NP-40) was added to a final concentration of 0.5%. Nuclei were pelleted and resuspended in buffer C (20 mM HEPES pH 7.5, 0.4 M KCl, 1 mM EDTA, 1 mM EGTA, 50 mM NaF, 5 mM Na orthovanadate 1 mM DTT and 1 mM PMSF). Both buffers contained 0.02 μg/μl of freshly prepared aprotinin and leupeptin. Supernatants were cleared by centrifugation after 15 min at 4°C and were frozen in aliquots at −70°C. The whole-cell extract was prepared by resuspending 1 g of cell pellet in 3 ml of buffer A (10 mM HEPES, pH 7.9, 10 mM $MgCl_2$, 1 mM DTT) and incubated for 30 min at 4°C. The cell suspension was then adjusted to 0.35 M KCl, the mixture was agitated gently for 20 min at 4°C and microfuged for 15 min at 4°C. The supernatant was collected, glycerol added to 20%, and stored at −70°C.

2.4. Production of antiserum specific for MIBP1 and RFX1

Rabbit antiserum was raised against an oligo-affinity purified MIBP1 protein from HeLa cells as described [7]. Rabbit antiserum to RFX was raised against N-terminal peptide as described previously [7,9].

2.5. Electrophoretic mobility shift assay

Mobility shift assays were performed as described previously [4,5]. 0.1 ng ^{32}P end labeled duplex oligonucleotide probe (approximately 10^4 cpm/lane) was incubated with 2 μl of nuclear extract (1 mg/ml protein) in 10 μl containing 10 mM HEPES pH 7.8, 75 mM KCl, 2.5 mM $MgCl_2$, 0.1 mM EDTA, 1 mM DTT, 3% Ficoll, and 1 μg poly(dI-dC). Where indicated, 2 μl of whole-cell extract (25 mg/ml protein) in 20 μl of the reaction mixture containing 10 mM Tris–HCl, pH 7.5, 100 mM KCl, 10 mM $MgCl_2$, 1 mM DTT, 1 mg poly(dI-dC) was used. In 'supershift' antibody experiments, the reaction mixture containing the nuclear extract was preincubated for 5 min at room temperature with 1 μl of either preimmune serum or serum raised against MIF-1 protein, before the addition of labeled oligonucleotide probe. The reaction mixture was incubated for 15 min at room temperature and analyzed by 4% PAGE as previously described.

2.6. Two-dimensional mobility shift/SDS′PAGE

The mobility shift assay was performed with whole-cell extract as described above (first dimension). The wet gel was subjected to autoradiography and the lanes containing the reaction mixture were excised and irradiated by UV light in the UV Stratalinker 1800 oven (Stratagene) using the auto-cross-link program for 10 min. The excised acrylamide slices were then placed on top of a 7.5% SDS–polyacrylamide gel, resolved by electrophoresis and subjected to autoradiography.

3. Results

3.1. Identification of a MIF-1-like sequence in the 5′ regulatory region of the c-myc gene

We identified a MIF-like sequence in the 5′ regulatory region of the human *c-myc* gene, designated 5′MIF (Fig. 1A). This 5′MIF sequence includes the GTTGCT motif that has been identified as an important contact point in the regulatory

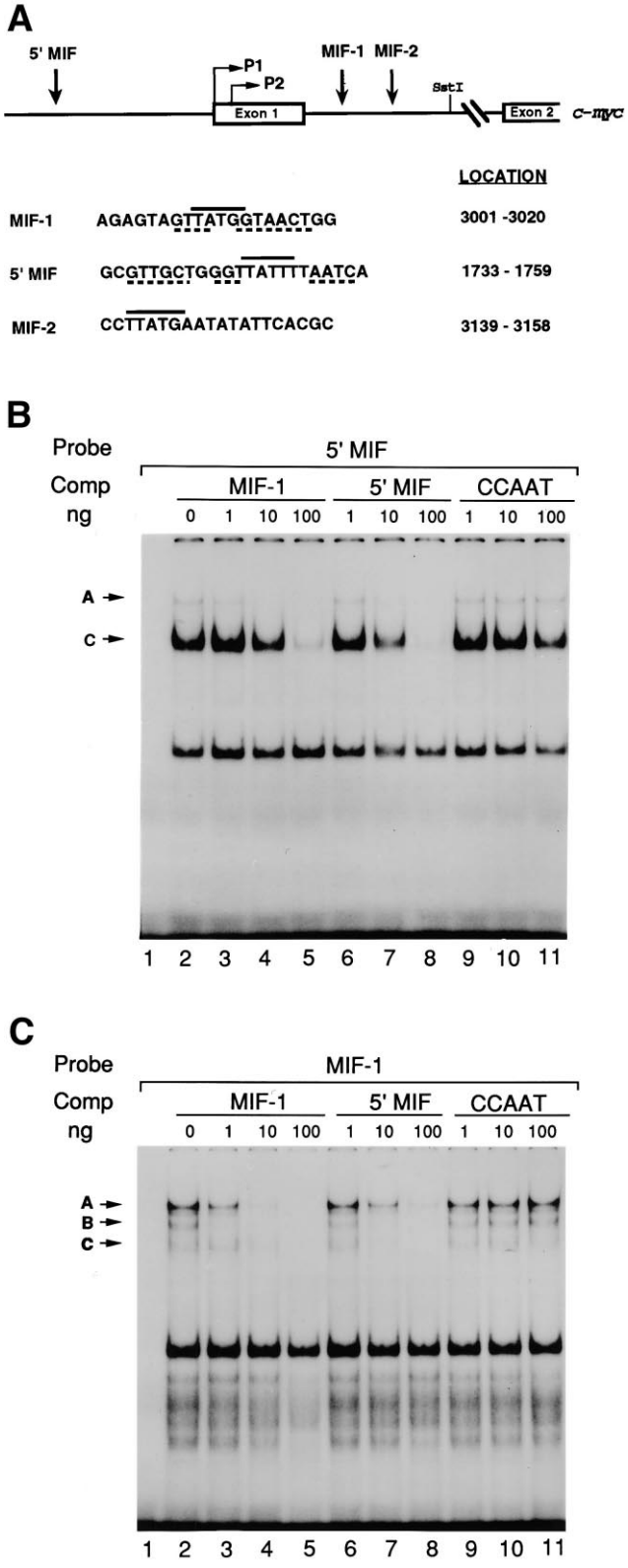

Fig. 1. MIF-1-like sequence within the 5′ regulatory region of the *c-myc* gene. A: Schematic representation of the MIF-1, MIF-2 and 5′MIF elements in the *c-myc* gene. The similarities between sequences are overlined and the binding motif [7] for MIBP1/RFX1 is shown in dashed line. B: Cross-competition analysis of the 5′MIF binding activity with the MIF-1 oligonucleotide probe. C: Cross-competition analysis of the MIF-1 binding activity with the 5′MIF oligonucleotide probe. CCAAT represents a non-specific control oligonucleotide. Probe alone is shown in lanes 1 of both B and C.

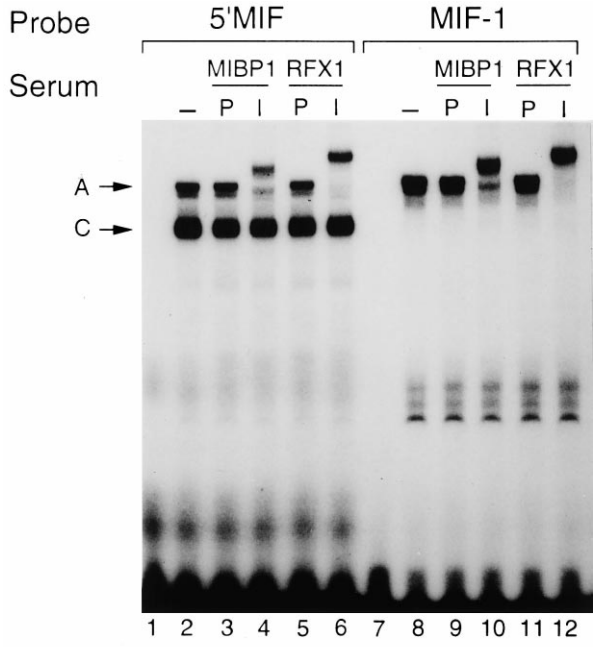

Fig. 2. anti-MIBP1 and anti-RFX1 sera recognize proteins in the 5′MIF complex. HeLa nuclear extracts were preincubated in the absence (−) or in the presence of either preimmune serum (P) or MIF-1 specific immune serum (I).

elements found in the enhancer and promoter region of HBV, Epstein Barr and polyomavirus [8,19–22] that bind similar protein factors as the *c-myc* (MIF-1) site [4,7]. To test whether the 5′MIF site binds similar protein factors, we constructed synthetic oligonucleotides representing the 5′MIF sequence and compared MIF-1 and 5′MIF as probes and competitors in the mobility shift assay (Fig. 1B,C). We observed two DNA–protein complexes formed with the 5′MIF probe, which comigrated with the 'A' and 'C' complexes at the MIF-1 site (Fig. 1B,C). Complex 'A' was more abundant at the MIF-1 site, while complex 'C' was more abundant at the 5′MIF site. DNA–protein complex formation could be blocked with each probe (Fig. 1B,C lanes 1–8) but not with unrelated sequences (Fig. 1B,C lanes 9–11).

To examine whether the MIBP1/RFX1 proteins which give rise to complex 'A' at the MIF-1 site [7] also interact specifically with the 5′MIF sequence, we tested the effect of anti-MIBP1 and anti-RFX1 sera on the migration pattern of the 5′MIF–protein complexes. We observed that both anti-MIBP1 and anti-RFX1 serum specifically retarded the migration of the 'A' complex at both the MIF-1 and 5′MIF probes (Fig. 2 lanes 4, 6, 10 and 12), while the control preimmune serum had no effect (Fig. 2 lanes 3, 5, 9 and 11). The 'supershift' of the 'A' complex was identical between the two probes used (Fig. 2), suggesting that MIBP1 and RFX1 bind to the *c-myc* 5′MIF site as well. The MIBP1 and the RFX1 antisera, however, did not supershift the 'C' complex (Fig. 2).

3.2. Similarity between DNA–protein complex formed at MIF-1 and 5′MIF to the MIF-2 complexes

We previously identified a 20 bp sequence located adjacent to the MIF-1 site in intron I of the *c-myc* gene, designated MIF-2 [5]. Since we also observed that a MIF-1 oligonucleotide competes for MIF-2 binding [4,5], and since the migration pattern of the DNA–protein complexes at the MIF-2 site resembled the migration of the 'C' complex formed at the MIF-1 and 5′MIF sites, we compared the migration pattern between the MIF-1, MIF-2 and 5′MIF complexes (Fig. 3A). We observed that complex 'C' which formed with both the MIF-1 and 5′MIF oligonucleotides also comigrated with the DNA–protein complex formed with the MIF-2 sequence (Fig. 3A). To demonstrate the relative abundance of these complexes, we used an equal amount of cell extracts (2 μg) for each probe, which resulted in a weaker signal at the MIF-1 site. Cross-competition analysis demonstrated that unlabeled MIF-2 oligonucleotides competed with complex 'C' at the 5′MIF sequence (Fig. 3B lanes 1–3), and conversely 5′MIF oligonucleotide competed protein binding at the MIF-2 site (Fig. 3B lanes 4–6). In addition, comparison of the nucleotide sequences revealed a C/GTTATG/T motif in the MIF-1, MIF-2 and 5′MIF sites. These results suggest that the MIF-2 binding polypeptide(s) may also interact with the adjacent MIF-1 site as well as with the upstream 5′MIF protein binding sequence.

3.3. Identification of polypeptides associated with MIF-2 and the 5′MIF binding activity

To identify polypeptides associated with MIF-2 and 5′MIF binding activity, HeLa whole-cell extracts were incubated either with 5′MIF or MIF-2 oligonucleotide probes and the resulting DNA–protein complexes were separated by native electrophoresis. The lanes containing the retarded protein complexes were excised, UV irradiated to cross-link the proteins to the oligonucleotide probe, and the gel slice was embedded onto a SDS–polyacrylamide gel, subjected to electrophoresis and autoradiography. Using this method we

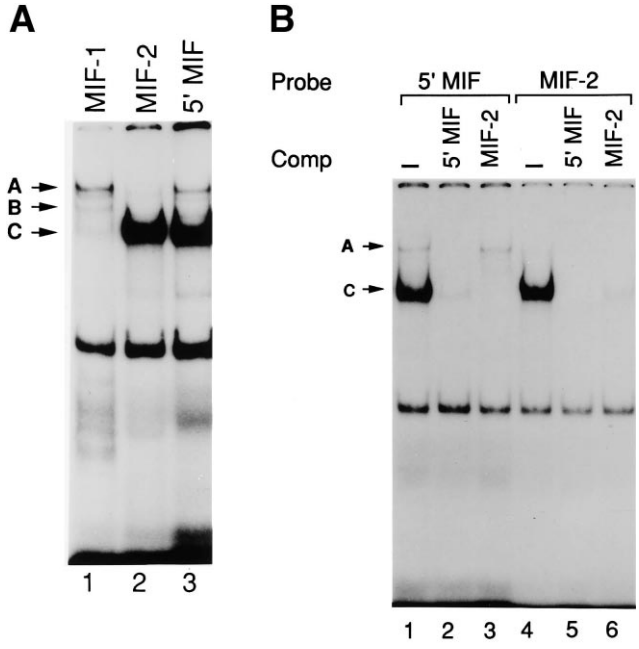

Fig. 3. MIF-1 and 5′MIF elements in the c-*myc* gene bind MIBP1/RFX1 and the MIF-2 binding proteins. A: Analysis of DNA–protein complexes from HeLa whole-cell extracts formed with MIF-1, MIF-2 and 5′MIF recognition sites. B: Cross-competition analysis of DNA–protein complexes formed at MIF-2 and 5′MIF sites.

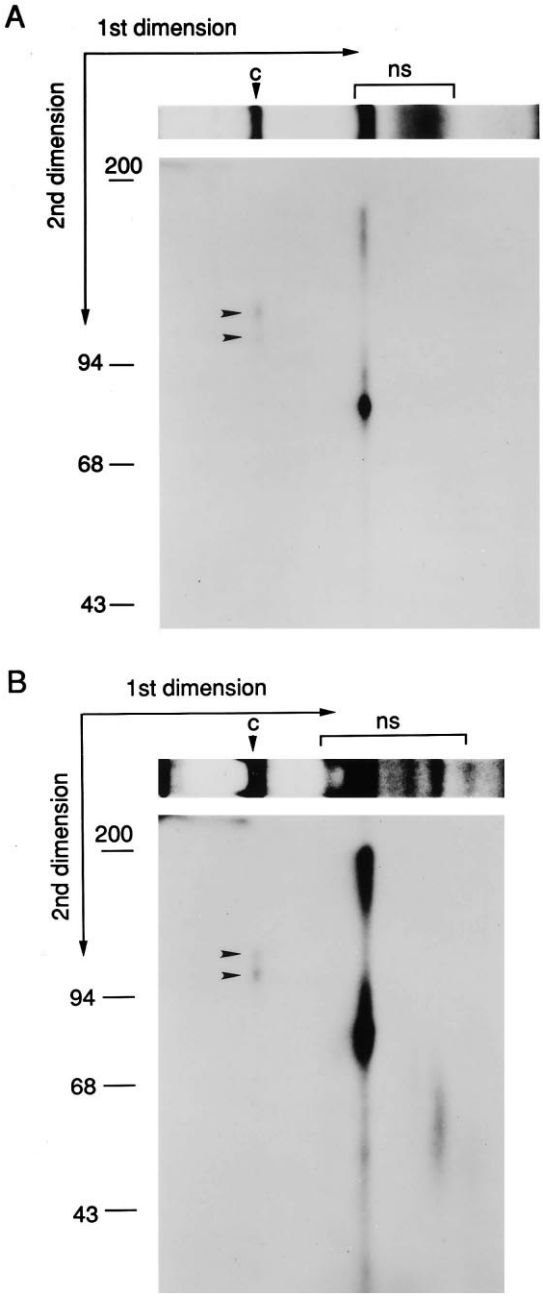

Fig. 4. Two-dimensional mobility shift SDS–PAGE. A: Mobility shift assay was performed using 5′MIF oligonucleotide probe (first dimension). B: Mobility shift using MIF-2 probe. The lane representing the DNA–protein complexes was cut from the mobility shift gel and was overlaid onto a 7.5% SDS–PAGE. DNA–protein complex 'C' and non-specific (ns) complexes are marked by arrowhead. The arrows depict two proteins, p105 and p115. Molecular weight markers are indicated.

identified two proteins, p105 and p115, which were detected in the 'C' complex at the 5′MIF site (Fig. 4A) as well as at the MIF-2 site (Fig. 4B). We found that p115 predominates over the p105 in the 5′MIF complex (at a ratio of 5:1) while the reverse is observed for the MIF-2 complex (at a ratio of 1:2). Our results suggest that MIF-1 and 5′MIF oligonucleotide probes are bound by MIBP1/RFX1 as well as the p105/p115 proteins. The MIBP1/RFX1 complex, however, preferentially recognized the MIF-1 site while the 115/105 proteins showed greater affinity for 5′MIF and MIF-2 sequences (Fig. 3A).

3.4. Repressor activity of the MIF-2 element in HeLa cells

To test, whether the MIF-2 and 5′MIF recognition sites mediate transcriptional regulation we prepared synthetic multimers of either MIF-2 or 5′MIF and cloned these multimers in the *Bgl*II site of the pCAT-P vector [7,15]. The parental control plasmid and constructs containing the MIF-2 and 5′MIF element clones in either sense or antisense orientation (in relation to the transcriptional unit of the SV40 promoter) were transfected into HeLa cells and CAT activity was measured 42 h after transfection. We observed that the constructs

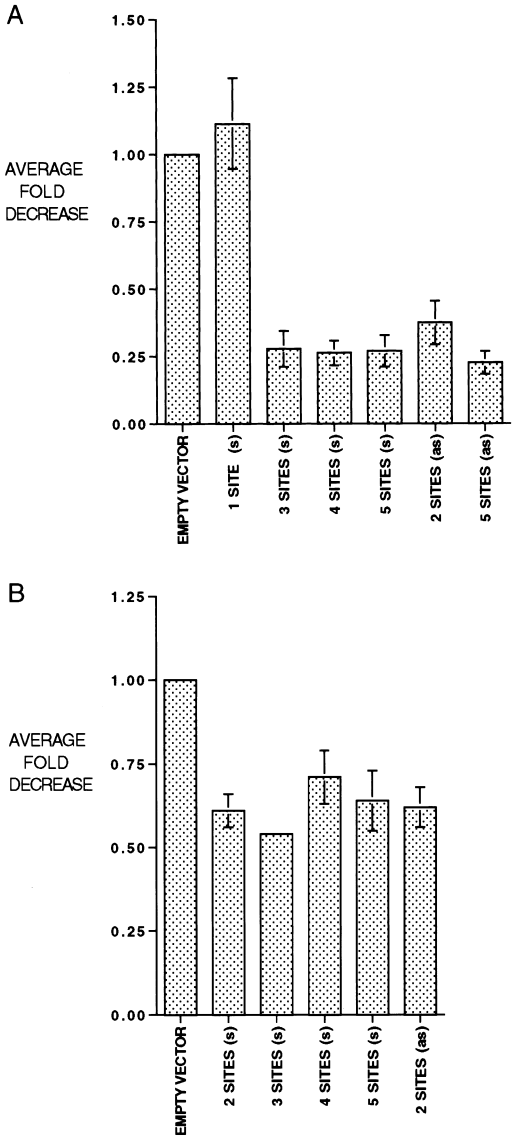

Fig. 5. Analysis of promoter activity by MIF-2 and 5′MIF sequences. Single copy or multimerized sites were cloned into an SV40 CAT expression vector in the *Bgl*II site in the proximity of the SV40 promoter [7,15]. A: CAT activity after transfection of MIF-2 sites. B: CAT activity after transfection of 5′MIF sites. Bar graphs show analysis of three independent experiments each performed in duplicate in HeLa cells and adjusted for transfection efficiency by cotransfection with the pGL_2-luciferase vector. (s) and (as): sense and antisense orientation.

containing sense and antisense MIF-2 multimerized elements displayed about four-fold reduction in CAT activity (calculated as the mean value of six experiments) as compared to the parent vector (Fig. 5A). Two or three copies of MIF-2 sequence cloned either in antisense or sense orientation, respectively, were sufficient to downregulate SV40 promoter activity while a single copy of the MIF-2 sequence had no effect (Fig. 5A). In contrast, the 5′MIF element was not active in HeLa cells even in multimerized form (Fig. 5B). These and previous data [7] suggest that the MIF-1 and MIF-2 sequences play a direct role in the regulation of transcription while the 5′MIF sequence may help to bring protein factors within the transcriptional initiation site.

4. Discussion

MIF-1 was initially identified as a binding activity that associated with a 20 bp sequence in the intron I of the *c-myc* gene and was shown to consist of two polypeptides, the MIBP1 and the MHC class II promoter binding protein RFX1 [4,6,7,14]. MIF-1-like binding sequences were also found in the regulatory regions required for promoter and enhancer activities of MHC class II genes and of several distinct DNA viral genes, including the HBV, CMV, EBV and Py genes [7,10,23]. Based on the previously established consensus sequences [7] we detected a MIF-1-like site, termed 5′MIF, within the 5′ untranscribed regulatory region of the *c-myc* gene. Moreover, we showed that this 5′MIF site also binds the MIBP1/RFX1 protein complex. Thus, the two *c-myc* promoters, P1 and P2, are flanked by MIF *cis* elements that interact with the same protein factors.

The MIBP1/RFX1 proteins comprise the retarded complex 'A' at both the MIF-1 and the 5′MIF sites. Since the other two DNA–protein complexes 'B' and 'C' also showed a similar migration pattern between the MIF-1 and 5′MIF, we tested whether they bound the same protein factors. We were interested in complex 'C' because of its relative abundance at the 5′MIF site and also because complex 'C' comigrated with both the MIF-1 probe and with the adjacent MIF-2 protein recognition sequences [7]. We identified two proteins in the 'C' complex, termed p105 and p115, and demonstrated that these two proteins can bind to all three MIF-1-like recognition sequences. Low abundance of the 'B' complex did not allow us to identify its protein composition, however, it was suggested previously that the 'B' complex may consists of other related members of the RFX gene family [24]. Our results demonstrate that MIBP1/RFX1 gives rise to the 'A' complex at both the MIF-1 and 5′MIF elements while p105/p115 gives rise to the 'C' complex formed at all three binding sites, MIF-1, 5′MIF and MIF-2.

Although the MIBP1/RFX1 and p105/p115 complexes can both bind the MIF-1 and 5′MIF sequences, the ratio between the 'A' to 'C' complexes varied significantly between MIF-1 and 5′MIF sites. The MIBP1/RFX1 complex binds with higher affinity to the MIF-1, while the p105/p115 complex was more abundant at the 5′MIF site. This preferential recognition of the MIBP1/RFX1 vs. p105/p115 complexes may be due to the location of the C/GTTATG/T motif in the MIF-1, MIF-2 and 5′MIF recognition sequences (overlined in Fig. 1A). For example, the GTTATG sequence overlaps with the palindromic MIBP1/RXF1 binding site in the MIF-1 recognition sequence, thus a high affinity binding of the MIBP1/RFX1 may create steric hindrance for p105/p115 binding. In contrast, the GTTATT motif in the 5′MIF site is situated between the two palindromic sites, thus making it more accessible for p105/p115 binding. Interestingly, only MIBP1/RFX1 complex can form at the EP element of the HBV enhancer region and in the X-box sequence in the promoter of the MHC class II gene [7] since the TTATG/T motif is not present in these regulatory sites. Such differential recognition of MIF's, EP and X-box sequences by either MIBP1/RFX1 or p105/p115 complexes may lead to differential regulation of the promoter activity in the *c-myc*, HBV or MHC class II genes.

Simultaneous binding of MIBP1/RFX1 and p105/115 proteins to all three sites that flank the promoter region of the *c-myc* gene, may play both structural and functional roles by bringing regulatory molecules into the vicinity of the transcription start site. It has been proposed that the RFX1 homodimer, which has two independent DNA-binding domains, could interact simultaneously with two different binding (X-box) sequences located far apart on the MHC class II DR gene [9]. Such interactions would cross-link the sites, thus bringing regulatory sequences into the vicinity of the transcription initiation site. A similar model has been described for the PRDII-BF1 protein containing two widely separated zinc finger motifs that could bind simultaneously to two copies of the same recognition sequence in the β-interferon gene [25]. Similarly, we have now identified several MIF sites flanking the promoter of the *c-myc* gene. The 5′MIF sequence is located 600 bp upstream from the initiation start site (P2 promoter) while MIF-1 and MIF-2 sequences are located 400 and 500 bp, respectively, downstream from the initiation start site. Thus, the observation that these widely dispersed elements may bind similar protein factors suggests a model in which MIBP1/RFX1 and p105/p115 may play a role to link the 5′MIF site to MIF-1 and MIF-2 sites leading to formation of a loop, and thus bringing regulatory sequences situated far upstream and downstream within the vicinity of the transcription initiation start site. Additional support for this model comes from the observation that both MIF-1 and MIF-2 but not the 5′MIF sequences contain intrinsic transcriptional activity, again suggesting that 5′MIF sequence may play a structural role in promoter topology.

We have previously shown that multimerized MIF-1 sequences act as silencers regulating the SV40 promoter in an orientation and position independent manner while one copy of MIF-1 sequence had no effect [7]. Similarly, to exhibit transcriptional repression tandem MIF-2 repeats downregulated SV40 promoter activity, while one copy of MIF-2 sequences had no effect. Similar results were reported in other studies of the SV40 enhancer where a single binding site which works in conjunction with the adjacent cis acting sites did not exhibit transcriptional activity, but could be active in dimerized or multimerized form [26,27]. These studies suggested that the interaction between cooperating *cis* acting elements and their binding factors could be compensated by the duplication of a functional site which could then interact with itself to regulate transcription. The MIF-1 site is located adjacent to three additional protein binding elements in intron I of the *c-myc* gene and it has been proposed that these sites work together to regulate promoter activity [5]. Thus, isolation of the genes that encode MIBP1, p105 and p115 would allow to study the cooperation of these binding factors and to examine

their role in the regulation of *c-myc*, MHC class II and viral gene expression.

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