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Synergistic activation of the *mkp-1* gene by protein kinase A signaling and USF, but not c-Myc

Anette Sommer[a,1], H. Burkhardt[a], Steven M. Keyse[b], Bernhard Lüscher[a,*]

[a] *Institut für Molekularbiologie, Medizinische Hochschule Hannover, Carl-Neuberg Strasse 1, 30625 Hannover, Germany*
[b] *ICRF Molecular Pharmacology Unit, Biomedical Research Centre, Ninewells Hospital, Dundee, UK*

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Abstract Mitogen-activated protein kinase phosphatase 1 (MKP-1) is negatively regulating mitogen-activated protein kinases and is therefore involved in early signaling processes. The expression of the *mkp-1* gene is induced by growth factors and stress. The promoters of the human and murine *mkp-1* genes contain several conserved DNA binding elements, including two cAMP response elements and an E box. We observed that the upstream stimulatory factor (USF), but not c-Myc, activated *mkp-1*. USF synergized with protein kinase A, thus providing evidence for a role of the E box, during signal-regulated stimulation of *mkp-1*.

Key words: Mitogen-activated protein kinase; Mitogen-activated protein kinase phosphatase 1; Upstream stimulatory factor; Myc; Protein kinase A; Signaling

1. Introduction

Early cellular signal transduction in response to serum growth factors is characterized by the rapid activation of different kinases, including mitogen-activated protein kinase (MAPK) family members and protein kinase A (PKA) [1,2]. These kinases phosphorylate several transcription factors that translate the incoming signals into regulation of gene transcription. The activities of MAPKs are opposed by MAPK phosphatases (MKPs). MKPs are dual specificity phosphatases that inactivate MAPKs by dephosphorylating both Thr and Tyr residues within their signature sequence [3]. Thus MKPs are negative regulators of MAPK-dependent signaling. The analysis of MKP-1, the ubiquitously expressed founding member of this family of phosphatases, revealed that it can efficiently dephosphorylate p42/44^{MAPK} (ERK1 and ERK2, respectively) in vitro and in vivo [4–6]. In addition, overexpression of MKP-1 blocks entry into the S phase and the expression of genes that are stimulated by p42/44^{MAPK} [7]. Thus, these findings suggest that MKP-1 antagonizes the function of p42/44^{MAPK}. In support, the inhibition of MKP-1 expression leads to a sustained activation of p42/44^{MAPK} [8–10].

The *mkp-1* gene, originally named erp/3CH134 or CL100, was first identified because it is induced by growth factors and stress [11–13]. Furthermore, it was demonstrated that PKA, Ca^{2+} and, to a lesser degree, protein kinase C (PKC) contribute to the activation of *mkp-1* [9–11,13]. In particular cholera toxin and the phosphodiesterase inhibitor isobutylmethylxanthine, which both elevate intracellular cAMP levels, strongly induce the expression of murine *mkp-1* [11,13]. PDGF-stimulated induction of MKP-1 was also abolished by a PKA inhibitor (PKI) [14]. Furthermore, Ca^{2+} was identified to play an essential role in the activation of *mkp-1* expression [10,15]. An increase in the level on intracellular Ca^{2+} leads to the stimulation of Ca^{2+}/calmodulin-dependent kinases which in turn can activate transcription factors that bind to cAMP response elements (CRE) [16]. Together these findings suggest that *mkp-1* is regulated via the cAMP signal transduction pathway. In addition, activation of p42/44^{MAPK} is important in stimulating the expression of MKP-1 [9,10].

Comparison of the 5′ flanking sequences of the murine and human *mkp-1* genes revealed a high degree of sequence homology in the proximal promoter region (roughly the first 250 nucleotides). Most notable are the presence of several conserved consensus sequences that include two CREs and one E box motif (Fig. 1) [13,17]. Further distal promoter regions show little homology. The analysis of the human *mkp-1* promoter demonstrated that a fragment of 800 bp, including the conserved region, was responsive to serum [17]. However, neither the human nor the murine *mkp-1* promoters contain serum response elements as found in many immediate early genes [18]. This suggests that the different stimuli described above, including p42/44^{MAPK}, work through the CREs.

Since the induction profile of *mkp-1* and c-myc are comparable in response to serum [11,13,19,20], we were interested in determining whether c-Myc participates in the regulation of the *mkp-1* promoter. c-Myc is a member of the basic region/helix–loop–helix/leucine zipper (bHLHZip) family of transcriptional regulators that interact with E box elements with the core sequence 5′-CACGTG (referred to as Myc E box) [21]. Several Myc-responsive genes have been identified that all contain E box DNA elements [22]. Our findings reveal that c-Myc cannot transactivate the *mkp-1* promoter. Instead upstream stimulatory factor (USF), a ubiquitously expressed bHLHZip protein that binds to Myc E boxes, was found to activate the *mkp-1* promoter. Furthermore, USF cooperated with signals that stimulate CRE-dependent transcription. These findings identify a novel cooperativity between CRE- and E box-mediated transcription.

*Corresponding author. Fax: (49)-511-532 4283.
E-mail: luscher.bernhard@mh-hannover.de

[1] Present address: Research Laboratories, Schering AG, Müllerstr. 178, 13342 Berlin, Germany.

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hu-mkp1   -227 GGACAGCAGGGCGGGGGCCGGGC-GCGAGCCAGCGCGCGGCGAGCGGACCCAGCTCCGAG
mu-mkp1   -245 GGACAGGAGGGTGGGGGCCGGGCTGCGAGCCAGCGCTCAG--AGCCGAGAG-GCTCCTAG
               ****** **** ********** ********** * *  *** **    ***** **
                      CRE                                        CRE
hu-mkp1   -168 GCTGATGACGTCTCCCCCTCTGGCTCGGCGGCGCCTGGCCTGGCAGGGCGGGTGACGTCA
mu-mkp1   -188 GCCGATGACGTCTTTGCTTTTGGCTTTGCGGCGCCAAGCTCGGTAGG-CGGGTGACGTCA
               ** **********   * * *****  ********  **  ** *** ***********
                         E box
hu-mkp1   -108 CCGCCCCGTCACGTGATCACCATTCAA-CAAACAC--------------CCCCCTCCCCC
mu-mkp1   -129 CCGCCCGGTCACGTGTCTGCCATTCAAACAAACAAACCGTTCTCCCCCACCCCCACCCCA
               ****** ********    ******** ******            ***** ****
                                                    TATA box
hu-mkp1    -63 TGAGAGGGGTCTGGCCAGC-CCCGT---CCCCCAGAGGCCGCATATAAACGCGCTCCCCG
mu-mkp1    -69 CCCCCCGCTTCTGTGCCGCGCCCGGGACCCCCGAGAGGCTACATA-AAACGCTC-CGTCG
                  *  ****  * ** ****    **** ******  **** ****** * *  **
hu-mkp1     -7 GCCAGGCTCGCTGCGAAGGAC
mu-mkp1    -11 GACGAGCGCGCAGTGAAGGAC
               * *  ** *** * *******
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Fig. 1. Sequence alignment with Clustal W of the mu-*mkp-1* (GenBank accession number S64851) [13] and the hu-*mkp-1* promotors (GenBank accession number U01669) [17]. The conserved DNA binding motifs of the E box, the two CRE sites and the TATA box have been highlighted in the sequence. Asterisks identify identical nucleotides. Arrow heads indicate the transcriptional start sites: the shaded arrow heads indicate the two G nucleotides identified by Lewis and Keyse (data not shown), the filled arrow heads indicate the site mapped by Kwak et al. [17] of the hu-*mkp-1* gene and the open arrow head indicates a potential start site of the mu-*mkp-1* gene [13].

2. Materials and methods

2.1. Cells and plasmids

COS-7 cells were cultivated in Dulbecco's modified Eagle's medium and RK-13 cells in modified Eagle's medium, both supplemented with 1% penicillin/streptomycin and 10% fetal calf serum. pSP-maxp22, pCMV-hu-c-myc, and pM4-min-tk-luc, containing four Myc E boxes, have been described previously [23]. pCαEV encodes the α isoform of the catalytic subunit of PKA and was a kind gift from G.S. McKnight [24]. A plasmid encoding PKI was obtained from R.A. Maurer [25], the reporter p$(Gal)_4$-mintk-luc from R. Janknecht [26] and plasmids encoding Gal4-USF, human USF1 (pUHD-USF1) and a USF1 mutant with a deletion of the basic region (pUHD-USF1mutBR) from M. Eilers [27] and Gal4-Myc(1–262) from C. Dang [28].

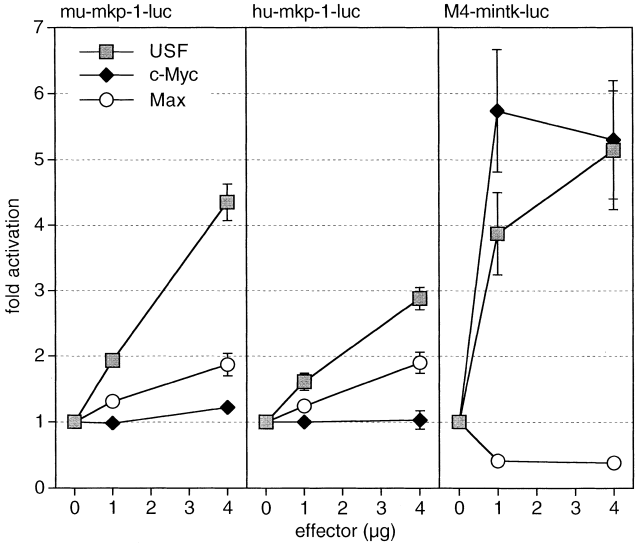

Fig. 2. USF but not c-Myc transactivates the mu-*mkp-1* and hu-*mkp-1* promotors. RK-13 cells were transiently transfected with 1 μg of mu-*mkp-1*-luc (left panel), hu-*mkp-1*-luc (middle panel) or M4-mintk-luc (right panel) in combination with the indicated amounts of expression plasmids coding for USF1, c-Myc or Max p22. The activities of the reporter plasmids in the absence of any coexpressed effector proteins were set as 1.

2.2. mkp-1 luciferase reporter constructs

A 255 bp long fragment from −245 to +10 of the murine *mkp-1* promotor which shows the highest sequence homology compared to the human *mkp-1* promotor [13,17] was amplified with the primers 3CH-*Bam*HI-FW (5′-CGGGATCCGGACAGGAGGGTGGGGGC-CG-3′) and 3CH-*Sal*I-REV (5′-GAAGATCTGTCCTTCACTGCG-CTGCCGTC-3′) on murine genomic DNA (kind gift of R. Lesche). The promoter fragment was cloned into the luciferase vector Xp-1 [29] and sequenced, resulting in the construct mu-*mkp-1*-luc. pGL3-151-luc comprises a 190 bp long fragment of the hu-*mkp-1* promotor from −179 to +11, referred to as hu-*mkp-1*-luc.

2.3. Transient transfections and electrophoretic mobility shift assays (EMSAs)

Transient transfections were performed using a standard calcium phosphate protocol as described previously [30,31]. All experiments were performed in duplicate or triplicate, repeated at least three times and standardized for coexpressed β-galactosidase activity. EMSAs were carried out as described previously [30]. The following oligonucleotides were used (the E box core sequences are underlined): CMD: 5′-TCA GAC CACGTG GTC GGG; hu-*mkp-1* E box: 5′-CCC CGT CACGTG ATC ACC (−105 to −88 in Fig. 1) and mu-*mkp-1* E box: 5′-CCC GGT CACGTG TCT GCC (−126 to −109 in Fig. 1).

3. Results

3.1. The mkp-1 promoter is responsive to USF but not to c-Myc

The human and murine *mkp-1* promoter possess a conserved E box (Fig. 1). Therefore, we analyzed whether these promoters are transcriptional targets for members of the bHLHZip family of transcription factors, in particular for c-Myc/Max and USF. In transient transfection experiments in RK-13 cells USF transactivated reporter gene constructs that contain the murine or human promotor in a dose-dependent fashion whereas c-Myc was inactive and Max resulted in a low level of activation (Fig. 2). In control experiments the standard Myc E box reporter M4-mintk-luc was activated by both c-Myc and USF and repressed by Max as described previously [23,32–35]. Thus, under standard transient transfection conditions c-Myc could not activate the *mkp-1* promoters. The lower level of stimulation of the *mkp-1*-derived reporters by USF1 in comparison to the artificial promoter

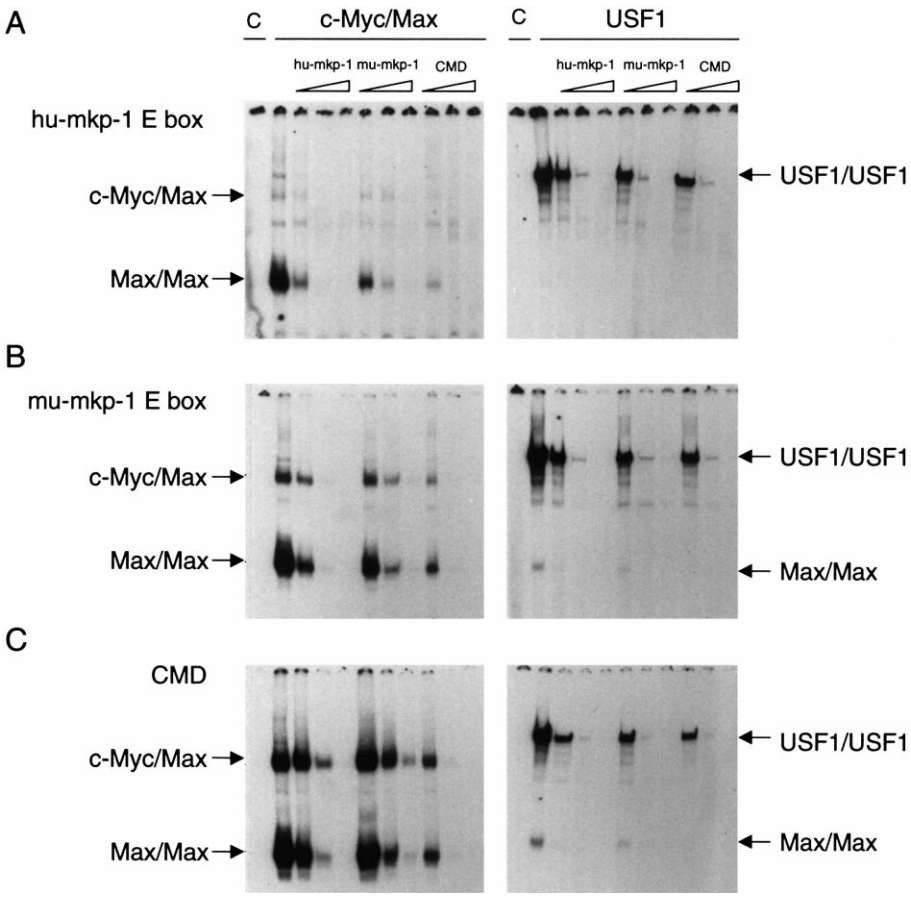

Fig. 3. DNA binding activity and affinity of COS-7-derived c-Myc/Max, Max/Max and USF1/USF1 complexes to oligonucleotides encompassing the E boxes of the hu- and mu-*mkp-1* promotors and the high affinity c-Myc E box oligonucleotide CMD. The following radioactively-labeled oligonucleotides were used: hu-*mkp-1* E box (A); mu-*mkp-1* E box (B) and CMD (C). The panels on the left show EMSAs with COS-7-derived c-Myc/Max and Max/Max complexes, the panels on the right show EMSAs with COS-7-derived USF1/USF1 complexes. (C) indicates control lanes where oligonucleotide probes without cell extracts were analyzed. Competition experiments were carried out with 5-fold, 50-fold and 500-fold excess of cold oligonucleotides as indicated. The free probes were run off the bottom of the gel for better separation of the protein–DNA complexes.

construct M4-mintk-luc is most likely due to the presence of only one E box in the former constructs whereas the latter contains four E boxes.

3.2. Poor binding of c-Myc/Max complexes to mkp-1-derived E boxes

Several studies have shown that the flanking sequences of E boxes affect the degree of binding by c-Myc/Max complexes, whereas USF/USF and Max/Max complexes are less sensitive. The sequences flanking the E boxes of the human and murine *mkp-1* promoters are conserved on the 5′ side but not on the 3′ side and, more importantly, these flanking sequences do not match high affinity consensus sequences (Fig. 1) (for review see [21]). Therefore, we studied in vitro DNA binding of COS-7-derived c-Myc/Max, Max/Max and USF1/USF1 complexes to oligonucleotides containing E boxes derived from the mu- and hu-*mkp-1* promotor in comparison to a high affinity c-Myc E box as in CMD (Fig. 3). The binding of the different complexes was assessed by using the three oligonucleotides as probes and by performing competition experiments with the same oligonucleotides. USF bound with a similar affinity to all three oligonucleotides (Fig. 3A–C, right panels). In contrast the binding of c-Myc/Max and, to a lesser degree, of Max/Max to mu-*mkp-1* and more significantly to hu-*mkp-1* was reduced compared to CMD (Fig. 3A–C, left panels). c-Myc/Max complexes were competed best with cold CMD followed by the mu-*mkp-1* and then the hu-*mkp-1* E box, whereas for USF1/USF1 CMD competed only marginally better than either the mu- or the hu-*mkp-1* E box. This reduced DNA binding activity of c-Myc/Max complexes to the E boxes derived from the *mkp-1* promoters is most likely sufficient for their inability to transactivate the *mkp-1* promoters as shown above.

3.3. USF and PKA cooperate in transactivation of the murine mkp-1 promoter

Not only the E box but also two CRE sites are conserved between the human and murine *mkp-1* promoters and multiple lines of evidence point to a role of the CREs in the regulation of the *mkp-1* genes by several different signal transduction pathways as summarized above. Therefore, we tested whether the mu-*mkp-1* promoter could be regulated by PKA. Coexpression of the catalytic subunit of PKA stimulated the activity of the promoter (Fig. 4A). Next we addressed the question whether PKA and USF cooperate on the mu-*mkp-1* promoter. Coexpression of different amounts of PKA and USF resulted in a synergistic activation of the reporter construct (Fig. 4A). The response to PKA was inhibited by a

dominant negative USF1 that lacks the DNA binding domain (Fig. 4B). Cooperativity with USF was also seen by stimulating endogenous PKA with forskolin, an adenylate cyclase agonist (Fig. 4C). Furthermore, coexpression of a PKI inhibited the activation of the mu-*mkp-1* promoter by USF (Fig. 4A). Transactivation through CREs is enhanced by CBP [1]. In agreement the cooperativity between PKA and USF was enhanced by CBP (Fig. 4D). Together these findings demonstrate that PKA-regulated factors cooperate with USF to synergistically activate the *mkp-1* promoter.

To address whether PKA directly regulated USF, its activity was measured in the presence or absence of coexpressed PKA on M4-mintk-luc, a reporter that contains four E boxes but no CRE. Transactivation by USF was not affected by PKA (Fig. 5A). Similarly, transactivation through the USF transactivation domain fused to the heterologous DNA binding domain of Gal4 was not responsive to PKA (Fig. 5A). These findings suggest that the cooperativity of PKA with USF is not due to direct regulation of USF by PKA but rather through activating CRE binding factors.

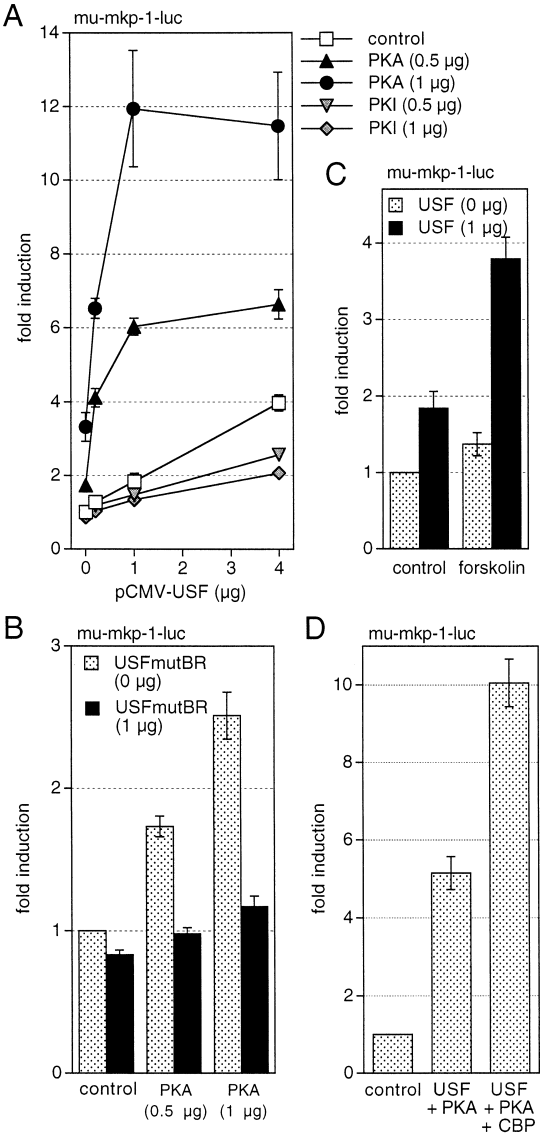

Fig. 4. USF cooperates with PKA in transactivating mu-*mkp-1*-luc. A: RK-13 cells were transiently transfected with mu-*mkp-1*-luc (1 µg) with the indicated amounts of expression plasmids encoding USF1, the catalytic subunit of PKA or PKI as indicated in the figure. B: RK-13 cells were transfected as in (A) with the indicated amounts of expression plasmids for the catalytic subunit of PKA and USF1mutBR. C: RK-13 cells were transiently transfected with mu-*mkp-1*-luc (1 µg), with or without 1 µg of pUHD-USF1. The cells were treated with 10 µM forskolin as indicated 14 h prior to harvest. D: RK-13 cells were transfected as in (A) with expression plasmids for USF1 (1 µg), PKA (0.5 µg) and CBP (2 µg) as indicated.

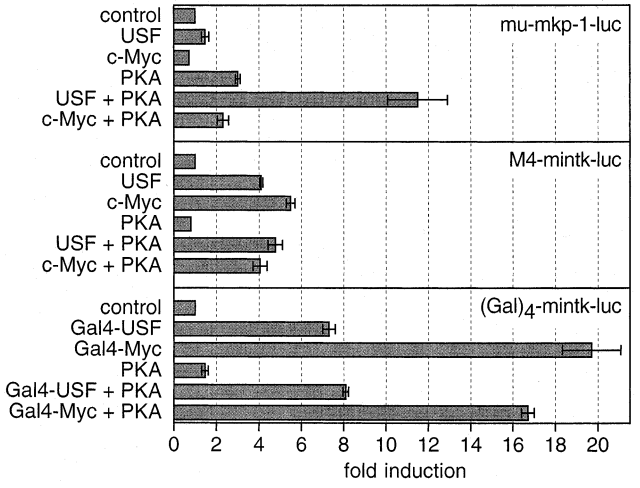

Fig. 5. USF and c-Myc are not targeted by PKA. RK-13 cells were transiently transfected with 2 g of mu-*mkp-1*-luc (top panel), M4-mintk-luc (middle panel) or $(Gal)_4$-mintk-luc (bottom panel). Expression plasmids for the following proteins were cotransfected as indicated: USF1 (1 g), the catalytic subunit of PKA (1 µg), c-Myc (1 µg), Gal4-USF (1 µg) and Gal4-Myc (0.1 µg). The control was set as 1 in each panel.

c-Myc was unable to activate the *mkp-1* promoter. However it remained open whether c-Myc can synergize with PKA. Therefore we coexpressed c-Myc with PKA and measured transactivation of mu-*mkp-1*-luc and M4-mintk-luc reporters (Fig. 5A). c-Myc did not alter the response of mu-*mkp-1*-luc to PKA and consistently PKA did not affect c-Myc-dependent activation of M4-mintk-luc. Similarly the activity of Gal4-Myc, a fusion protein of the Myc transactivation domain and the Gal4 DNA binding domain, was not affected by PKA (Fig. 5A). These findings support the notion that c-Myc is not directly involved in the transcriptional regulation of the *mkp-1* gene.

4. Discussion

Comparing the promotors of the murine and human genes coding for MKP-1 revealed a conserved Myc consensus E box and two conserved CRE sites (Fig. 1). We were interested in determining whether c-Myc is involved in regulating the expression of *mkp-1*. Expression of *mkp-1* mRNA and protein was stimulated as early as 30 min and 1 h, respectively, after applying different stimuli [9,11–13]. The expression of c-myc occurs with similar kinetics [19,20]. However c-Myc was unable to stimulate the *mkp-1* promoters (Fig. 2). This is, at least in part, the result of low DNA binding activity towards E boxes derived from either the human or the murine *mkp-1* promoters (Fig. 3). These experimental findings are in agreement with sequence comparisons of *mkp-1* E boxes with previously identified favorable and unfavorable sites for c-Myc/

Max binding (for review see [21]). While the core motif of both *mkp-1* E boxes is identical to the consensus (i.e. 5′-CACGTG), the flanking sequences are unfavorable for c-Myc/Max binding. In particular the position next to the core is important to define high affinity binding. While 5′-CCACGTGG provides a high affinity site, 5′-TCACGTGA, as found in hu-*mkp-1*, binds poorly to c-Myc/Max. In contrast USF/USF complexes bind to both sequences with similar affinity [36] which is confirmed by our EMSA analysis (Fig. 3).

From the proposed elements in the *mkp-1* promoter only the CREs are readily categorized as elements that can respond to different signaling cascades. In particular the responses to increases in Ca^{2+} and cAMP are mediated at least in part through CREs, but also the activation of MAPKs, e.g. by stimulating RSK2, can signal through CREs [16,37]. Thus, it is likely that proteins binding to CREs are targets of all different signaling cascades that have been shown to induce *mkp-1* expression. In contrast USF is a constitutively and ubiquitously expressed transcription factor. Little is known about its regulation by signaling cascades. However, recent findings have shown that USF is a phosphoprotein [38] that may be regulated in response to cadmium and H_2O_2 [39]. In addition USF1 has been shown to cooperate with interferon-γ-activated STAT1 in stimulating the expression of the MHC class II transactivator gene cIITA [40]. In the case of the gene encoding the α7 subunit of the α-bungarotoxin-sensitive nicotinic acetylcholine receptor, USF cooperates with the early growth response gene transcription factor Egr-1, which is also targeted by phorbol ester signaling [41,42]. Together with our findings that USF1 cooperates with PKA in the activation of *mkp-1*, it appears that USF plays a role in several different signaling processes. It is possible that in all these situations USF is a constitutively present cooperating factor that promotes and facilitates transactivation by factors that are endpoints of signaling cascades, which is consistent with our finding that PKA does not directly regulate USF.

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