Cell Type-specific Inhibition of the ETS Transcription Factor ER81 by Mitogen-activated Protein Kinase-activated Protein Kinase 2* 

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Mitogen-activated protein kinase-activated protein kinase 2 (MK2) is an important intracellular mediator of stress signals. In this report, a novel target of MK2 has been identified, the ETS transcription factor family member ER81, whose dysregulation contributes to tumorigenesis and whose normal function is required during development. MK2 phosphorylates ER81 in vitro within its central inhibitory domain, and overexpression of MK2 leads to increased in vivo phosphorylation of ER81. Two serine residues, ER81 amino acids 191 and 216, were identified as MK2 phosphorylation sites. MK2 suppresses basal ER81-dependent transcription, and this suppressive effect is alleviated upon mutation of the MK2 phosphorylation sites in a cell type-specific manner. However, MK2 can also interfere with ER81-mediated transcription independently of serine 191 and serine 216 phosphorylation. Furthermore, MK2 overexpression counteracts the stimulation of ER81 activity by p38 mitogen-activated protein kinase. Altogether, MK2 may regulate ER81 transcriptional activity in a cell type-specific manner and thereby modulate various physiological processes beyond stress responses.

Three mitogen-activated protein (MAP) kinase classes exist in the mammalian cell, the growth factor-activated ERK-MAP kinases and two stress-activated protein kinase families, JNK and p38 (1). A plethora of stimuli, including serum, growth factors, cytokines, tumor necrosis factor-α, UV light, hyperosmolarity, and heat, trigger intracellular signal transduction pathways that lead to the activation of one or more of these MAP kinase classes. Upon activation, MAP kinases functionally regulate many proteins through serine/threonine phosphorylation, including distinct MAPKAP kinases, which in turn phosphorylate and modulate downstream effectors.

In particular, MAPKAP kinase 2 (MK2) is stimulated by signals such as heat shock and tumor necrosis factor-α via the p38-MAP kinase pathway (2, 3). On the other hand, lack of MK2 activity severely dampens tumor necrosis factor-α biosynthesis, causing resistance to lipopolysaccharide-induced endotoxic shock (4). Furthermore, 5-lipoxygenase, which catalyzes important steps in the synthesis of a group of inflammatory mediators, leukotrienes, is a downstream target of MK2 (5), suggesting that MK2 may affect the inflammatory response at different levels.

A variety of other proteins are phosphorylated by MK2, implicating the involvement of MK2 in many different physiological processes dependent on these target proteins. Among those are the small heat shock proteins (6), the F-actin-binding lymphocyte-specific protein 1 (7), serum response factor that is involved in the regulation of the c-fos proto-oncogene (8), and the transcription factor CREB, which can be phosphorylated by MK2 upon fibroblast or nerve growth factor stimulation (9, 10).

ER81 is a transcription factor of the ETS protein superfamily that is characterized by a highly conserved DNA binding domain (11). Gene regulation mediated by ER81 is dependent on its N- and C-terminal transactivation domains, which may be modulated by a central inhibitory region. In addition, transcriptional activity of ER81 can be stimulated by ERK-MAP kinases (12). Analysis of mouse embryos revealed a spatially and temporally controlled ER81 expression pattern, suggesting that ER81 may serve important functions during development (13). Also, knock-out ER81 mice display severe motor discoordination because of the improper establishment of nerve connections in the developing spinal cord (14). Furthermore, ER81 overexpression may contribute to the development of breast cancer, and a chromosomal translocation involving the ER81 and EWS genes results in the generation of Ewing’s sarcoma (15, 16).

In this report, ER81 is identified as a novel target of the protein kinase MK2. By phosphorylating ER81 on two serine residues, MK2 can inhibit ER81 transcriptional activity in a cell type-specific fashion. Furthermore, MK2 may additionally interfere with ER81-mediated transcription in a manner independent of ER81 phosphorylation by MK2.

EXPERIMENTAL PROCEDURES

Kinase Assays—The cells grown on 6-cm dishes were transfected with HA- or Myc-tagged protein kinase expression vectors. 36 h after transfection, the cells were washed with 2 ml of phosphate buffered saline. All subsequent procedures were performed at 4 °C. The cells were lysed for 5 min with 600 μl of 1× Frakcelton buffer (10 mM Tris, 30 mM Na3P2O7, 50 mM NaCl, 50 mM NaF, 1% Triton X-100, pH 7.1) supplemented with 10 μg/ml leupeptin, 2 μg/ml aprotime, 1 μg/ml pepstatin A, 1 mM phenylmethylsulfonyl fluoride, 0.5 mM Na2VO4, 2.5 mM sodium β-glycerophosphate, 0.2 mM dithiothreitol. After scraping of the dishes, the cell lysate was transferred to a 1.5-ml tube, vortexed for 15 s, and then tumbled for 45 min. Debris was removed by centrifugation (10 min, 2000 × g), and the supernatant was incubated with 30 μl of protein A-agarose beads (Repligen) for 45 min with continuous tumbling. After centrifugation (5 min, 20000 × g), 1 μl of appropriate mouse monoclonal antibody (α-HA, 12CA5; α-Myc, 9E10) was added to the supernatant, and 2 h later 25 μl of protein A-agarose bead slurry was added followed by another hour of tumbling. The beads were recovered...
by centrifugation (1 min, 960 × g) and then washed three times with 0.5 mM of lysis buffer. This was followed by two washes in kinase buffer (20 mM Hepes, pH 7.4, 10 mM MgCl₂, 25 mM NaCl, 10 mM sodium β-glycerophosphate, 0.1 mM Na₃VO₄, 0.2 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol, 10 μM ATP). Finally, the beads were resuspended in 40 μl of lysis buffer, of which 5 μl were utilized for in vitro kinase reactions. Typically, these were performed in a volume of 15 μl with 0.2–2 μg of substrate and 2 μCl of [γ-³²P]ATP (3000 Ci/mmol). The incubation time was 20 min at 30 °C, after which the samples were subjected to SDS-polyacrylamide gel electrophoresis. The gels were dried and exposed to x-ray film.

**Coimmunoprecipitation Assays**—Transiently transfected 293T cells were lysed in 0.25× Fracellton buffer supplemented with 10 μg/ml leupeptin, 2 μg/ml apro tin, 1 μg/ml pepstatin A, 1 mM phenylmethylsulfonyl fluoride, 0.5 mM Na₃VO₄, 0.2 mM dithiothreitol. Further processing was as described above, except that protein A-agarose beads were washed four times in lysis buffer and then taken up in 25 μl of 2× Laemmlli sample buffer. Also, a small aliquot of lysate (1 μl) was employed as substrates in in vitro kinase reactions. Typically, these were performed in a volume of 15 μl with 0.2–2 μg of substrate and 2 μCl of [γ-³²P]ATP (3000 Ci/mmol). The incubation time was 20 min at 30 °C, after which the samples were subjected to SDS-polyacrylamide gel electrophoresis. The gels were dried and exposed to x-ray film.

**Metabolic Labeling**—Transiently transfected cells grown on 6-cm dishes were labeled with 0.25 μCi/ml [³²P]orthophosphate for 4 h. Then cells were washed twice with 2 ml of phosphate-buffered saline and lysed in 1× Fracellton buffer supplemented with protease and phosphatase inhibitors as described above. Immunoprecipitations were performed with α-Myc (9E10) antibodies, and the immunoprecipitates were subjected to SDS-polyacrylamide gel electrophoresis. Western blotting was performed utilizing mouse monoclonal α-HA (12CA5) or α-Myc (9E10) antibodies. Finally, blots were developed with goat α-mouse antibodies or protein G coupled to horseradish peroxidase employing chemiluminescence.

**Phosphorylation of ER81 by MAP Kinases**—The ETS transcription factor ER81 has been shown to be phosphorylated by ERK-MAP kinases within amino acids 63–182 that are part of an N-terminal transactivation domain (12). To exclude that other regions of ER81 (Fig. 1A) become phosphorylated by any of the three MAP kinase classes, different GST-ER81 fusion proteins were employed as substrates in in vitro kinase assays utilizing immunoprecipitated ERK1, JNK1, or p38-2 (Fig. 1B). ERK1, when stimulated by the constitutively active Raf-1 kinase BXB (18), efficiently phosphorylated GST-ER81 63–182, but it phosphorylated none of the other GST-ER81 fusion proteins. Likewise, JNK1, when activated by a constitutively active MEK kinase, MEKKc (19), phosphorylated only GST-ER81 63–182 to a significant degree.

On the other hand, p38-2, which on its own was always activated to some degree, was apparently able to phosphorylate both GST-ER81 63–182 and GST-ER81 182–334 (Fig. 1B). As expected, phosphorylation of GST-ER81 63–182 by p38-2 was further enhanced by MEKKc (DD), a constitutively active activator of p38-2 (20). In stark contrast, phosphorylation of GST-ER81 182–334 was reduced upon coexpression of p38-2 and MEKKc (DD), suggesting that GST-ER81 182–334 was not directly phosphorylated by p38-2 but most likely by a p38-2-associated protein kinase whose activity in the p38-2 immunoprecipitate is reduced upon MEKKc (DD) expression.

**Phosphorylation of MK2**—Often, protein kinases can stably interact with their substrates. Thus, the above postulated p38-2-associated protein kinase might be a MAPKAP kinase that is phosphorylated and thereby activated by p38-2. A MAPKAP kinase that is thought to be a downstream target of p38-MAP kinases, but not of ERK- or JNK-MAP kinases, is MK2 (2). Therefore, it was tested whether MK2 specifically interacted with p38-2. Myc-tagged MK2 and HA-tagged ERK1, JNK1, or p38-2 were coexpressed in 293T cells, and α-HA immunoprecipitations were performed. The presence of coimmunoprecipitated MK2 was then assessed by α-Myc Western blotting (Fig. 2A). MK2 coimmunoprecipitated only with p38-2. A reverse order coimmunoprecipitation assay, α-Myc immunoprecipitation followed by α-HA Western blotting revealed the same in vivo interaction of MK2 with p38-2 (Fig. 2B). Importantly, coexpression of MEKKc (DD) suppressed the interaction of p38-2 with MK2 (Fig. 2B), which offers an explanation for the conundrum of why phosphorylation of ER81 by MK2 was not detected by autoradiography after gel electrophoresis.

**Results**

**Regulation of ER81 by MAPKAP Kinase 2**

**Fig. 1. In vitro phosphorylation of ER81.** A, schematic structure of murine ER81. The ETS domain mediates DNA binding. AD, activation domain. ID, inhibitory domain. B, HA-tagged MAP kinases (200 ng of ERK1, 100 ng of p38-2, or 200 ng of JNK1) were cotransfected with the indicated upstream activators (500 ng of BXB, 500 ng of MEKKc (DD), or 10 ng of MEKKc) into Mv1Lu cells and then immunoprecipitated with α-HA antibodies. These immunoprecipitates were incubated with [γ-³²P]ATP and the indicated GST-ER81 fusion proteins, phosphorylation of which was revealed by autoradiography after gel electrophoresis.
cells; at most, transcriptional activation was reduced to 50% (Fig. 4C). Again, ER81 protein levels were basically unaffected by MK2 overexpression in RK13 cells (Fig. 4D). In conclusion, MK2 can suppress ER81-dependent transcription strongly in MV1Lu cells and weakly in RK13 cells. However, it remains unresolved whether this suppression of ER81-dependent transcription requires the direct phosphorylation of ER81 by MK2, a question that can be answered upon identification and mutation of respective phosphorylation sites in ER81.

Mapping of Phosphorylation Sites—As a first step to identify the MK2 phosphorylation sites in ER81, phosphopeptide analyses were performed on ER81 amino acids 182–334 that are specifically targeted by MK2 as shown above. Thus, GST-ER81182–334 was phosphorylated with MK2 in the presence of [γ-33P]ATP. After SDS-polyacrylamide gel electrophoresis, the 32P-labeled GST-ER81182–334 protein was eluted from the gel and then digested with trypsin, and the resulting phosphopeptides were separated in two dimensions on thin layer chromatography plates as described (22). Three prominent phosphopeptides were observed (Fig. 5A, bottom panel), indicating that more than one MK2 phosphorylation site may exist. Please note that because of incomplete trypsin digestion, contamination with chymotrypsin, or incomplete oxidation of methionine and cysteine residues, the number of phosphorylation sites is often less than the number of phosphopeptides observed.

Full-length, Myc-tagged ER81 was also isolated from transiently transfected, 32P metabolically labeled 293T cells, and its tryptic phosphopeptide pattern was determined (Fig. 5A, top panel); five prominent phosphopeptides were observable, three of which comigrated with the peptides phosphorylated by MK2 in vitro (Fig. 5A, middle panel). These results indicate that MK2 phosphorylates ER81 at amino acids that are in vivo phosphorylation sites.

Recently, it has been shown that phosphopeptides a–c (Fig. 5A) correspond to in vivo phosphorylation of ER81 at serine residues 191 and 216 (23). Consistently, although mutation of either serine 191 or serine 216 to alanine did not abolish phosphorylation of GST-ER81192–214 by MK2, mutation of both serine residues did (Fig. 5B). Collectively, these data indicate that MK2 phosphorylates ER81 on serine 191 and serine 216.

**Basal Transcriptional Activity of the Alanine 191 and Ala- nine 216 Mutants**—To prevent phosphorylation at serine 191 and serine 216, these phosphoacceptor sites were mutated to alanine. Respective ER81 mutants were then compared in their transcriptional activity to the wild-type ER81 molecule. As shown in Fig. 6A and reported previously (23), the S191A, S216A, and S191A/S216A mutants activated the TORU-luc reporter 2.5-fold more than the wild-type ER81 molecule in MV1Lu cells; this is not due to higher amounts of the mutant proteins, because they were comparably expressed as the wild-type ER81 protein (Fig. 6B). These results suggest that phos-
Regulation of ER81 by MAPKAP Kinase 2

Fig. 5. Phosphorylation of serine 191 and serine 216 by MK2. A, mapping of ER81 phosphorylation sites. In vivo 32P-labeled 6Myc-ER81Glu191/Ser216, or GST-ER81Glu191/Ser216, labeled in vitro by MK2 were digested with trypsin, and the resulting phosphopeptides were separated by electrophoresis horizontally and by chromatography vertically. The middle panel depicts a mixture of the in vivo and in vitro phosphopeptides. B, in vitro phosphorylation of wild-type GST-ER81Glu191/Ser216, or the indicated serine to alanine point mutants thereof, by MK2. The bottom panel reveals comparable levels of the GST-ER81Glu191/Ser216 proteins by Coomassie Blue staining.

Fig. 6. Cell type-specific enhancement of basal transcription upon mutation of serine 191 or serine 216. A, impact of serine 191 and serine 216 phosphorylation on basal ER81 transcriptional activity. Wild-type 6Myc-ER81Glu191/Ser216 (50 ng) or the indicated alanine mutants thereof were expressed in the presence or absence of MK2 (20 ng) in Mv1Lu cells and activation of the TORU-luc reporter plasmid measured. B, a respective α-Myc Western blot showing levels of wild-type and mutant ER81 molecules in transfected Mv1Lu cells. C and D, analogous with RK13 cells.

Next, the ER81 mutants were also tested in RK13 cells (Fig. 6, C and D). Surprisingly, they did not behave differently from the wild-type ER81 molecule in the presence or absence of MK2. As shown already in Fig. 4C, MK2 overexpression also had little effect on ER81 transcriptional activity in comparison with Mv1Lu cells. Thus, ER81 activity appears to be cell type-specifically regulated by MK2.

Impact of MK2 on MAP Kinase-induced Transcription—ER81 has been shown to be activated upon ERK-MAP kinase stimulation (12). Thus, it was tested whether phosphorylation of serines 191 and 216 induces ER81 activity by ERK-MAP kinases. Whereas wild-type ER81 and the S191A/S216A mutant displayed a -2.5-fold difference in transcriptional activity in the absence of BXB, a constitutive active activator of ERK-MAP kinases (18), transcriptional activities were the same in the presence of BXB in Mv1Lu cells (Fig. 7A).

In addition, expression of MK2 only slightly affected BXB-triggered activation of ER81 and its S191A/S216A mutant. Interestingly, MK2 significantly reduced BXB-triggered transcription in the absence of ER81 (Fig. 7A, Vector), suggesting that an endogenous ETS factor(s) mediating this induction is affected by MK2.

ER81 is also a target of p38-MAP kinases. Therefore, p38-2-induced transcriptional activation of ER81 was also investigated. Whereas wild-type ER81 was ∼3-fold activated by p38-2, S191A/S216A transcriptional activity was raised by only approximately half in Mv1Lu cells (Fig. 7A). As a consequence of this different degree of activation by p38-2, the transcriptional activity of wild-type ER81 approached the same elevated level as the S191A/S216A mutant, contrasting their ∼2.5-fold difference in activity in the absence of p38-2. However, MK2 overexpression re-established the difference in transcriptional activity between wild-type and S191A/S216A ER81 by repressing wild-type ER81 more than the S191A/S216A mutant. Thus, ERK- and p38-MAP kinase-mediated activation of ER81 is differentially affected by MK2 expression.

Similar experiments with BXB, p38-2, and ER81 were performed in RK13 cells (Fig. 7B). Wild-type ER81 and the S191A/S216A mutant behaved similarly under all circumstances. In addition, MK2 overexpression had no effect on BXB-induced ER81 activity, whereas p38-2-mediated induction of ER81 was ∼3-fold suppressed by MK2.

DISCUSSION

In this report, it has been shown that MK2 can phosphorylate ER81 on two serine residues (amino acids 191 and 216) in vitro and in vivo. Analysis of the ER81 amino acid sequence surrounding serine 191 and serine 216 (FRRKL5191 and YQRKMS216) reveals that both of these two serines match the MK2 consensus site, a serine preceded by an arginine at position −3 and by a bulky hydrophobic residue at position −5 (24). Both serine 191 and serine 216 are localized within the central inhibitory domain of ER81 encompassing amino acids 182–249 (Fig. 1A), suggesting that MK2 phosphorylation may modulate the function of this inhibitory domain.

Indeed, mutation of serines 191 and 216 to alanine enhanced the basal transcriptional activity of ER81 in Mv1Lu cells, indicating that phosphorylation at these sites may suppress ER81 function. However, this differential activity of wild-type and S191A/S216A ER81 was not observed in RK13 cells. What could cause this cell type-specific behavior? One reason might be that phosphorylation of serine 191 or serine 216 is required for the recruitment of a corepressor, which is cell type-specifically expressed. Another potential explanation could be that the inhibitory domain of ER81 is masked and thereby function-
MK2 expression also led to strong (Mv1Lu cells) or weak (RK13 cells) transcriptional down-regulation of the S191A, S216A, and S191A/S216A mutants, indicating that MK2 operates via another pathway not involving serine 191 or serine 216 phosphorylation. Potentially, this could entail phosphorylation of ER81 by MK2 at another site. However, this appears to be unlikely because MK2 phosphorylates in vitro exclusively serines 191 and 216 in ER81 (Figs. 3A and 5B). Rather, MK2 might modulate a cofactor, either inhibiting its transactivation function or precluding its interaction with ER81, or sequester endogenous p38-MAP kinase (see below), whose intrinsic basal activity may therefore no longer contribute to the low level of basal phosphorylation and thus activation of ER81.

Upon stimulation of ERK-MAP kinases with BXB or upon overexpression of p38-2-MAP kinase, wild-type ER81 and the S191A/S216A mutant had the same transcriptional activity even in Mv1Lu cells. These data indicate that the inhibitory effect of endogenous MK2 in Mv1Lu cells can be overridden upon MAP kinase stimulation. Presumably, this involves direct phosphorylation of ER81 by MAP kinases, leading to a stimulation of its transactivation potential.

Overexpression of MK2 counteracted the stimulation of wild-type ER81 and the S191A/S216A mutant by p38-2 in both Mv1Lu and RK13 cells. One reason for this may be the sequestration of p38-MAP kinases by MK2. Several experimental data support such a hypothesis: (i) MK2 was shown to coimmunoprecipitate with p38, which is consistent with two other reports describing an interaction between these two protein kinases (25, 26). Interestingly, other protein kinases may be associated with the MK2-p38 complex. For instance, MK2 and p38 are in a complex with the protein kinase Akt before and after stimulation of human neutrophils, allowing the phosphorylation of Akt by MK2 (26). Yet, this complex formation may be cell type-specific, because Akt activation appears not to be mediated by MK2 in 293 cells upon IFG-1 stimulation or in Swiss 3T3 cells upon stimulation with various stressors (27, 28). Thus, MK2, potentially in conjunction with other proteins, can form a complex with p38-MAP kinases, a prerequisite for sequestration. (ii) Whereas the classical ERK-MAP kinases predominantly reside in the cytoplasm before stimulation and in part translocate to the nucleus after stimulation (29), p38-MAP kinases are predominantly nuclear in unstimulated cells. Upon stimulation, this intracellular localization has been reported to remain unchanged, or cytoplasmic accumulation of p38 has been observed in different cell lines (25, 30, 31). Cytoplasmic accumulation is dependent on a limiting factor, which has been identified as MK2 (25), indicating that MK2, which upon phosphorylation by p38 is indeed exported from the cell nucleus (25, 32), coexports p38-MAP kinase. Accordingly, coexpression of p38-2, which is active to some degree even without stimulation (20), with MK2 leads to the phosphorylation of MK2 by p38-2, nuclear coexport of p38-2 and consequently to a reduced activation of the nuclear ER81 protein by p38-2. Because MK2 does not interact with ERK-MAP kinases, MK2 overexpression suppresses barely, if at all, ER81 activity induced by the specific upstream activator of ERK-MAP kinases, BXB.

In addition to ER81, other transcription factors have been shown to be phosphorylated by MK2: the MADS box protein serum response factor (8, 33), the basic helix-loop-helix transcription factor E47 (34), and the basic leucine zipper protein CREB (9, 10). Serum response factor is pivotal for the regulation of the immediate-early gene c-fos and is phosphorylated in vivo on serine residue 103, which increases its DNA binding activity. Several protein kinases have been implicated in serine 103 phosphorylation, including casein kinase II, the growth factor-inducible kinase p90(SH), Ca2+/calmodulin-dependent protein kinase II, and MK2 (8, 35–37). However, hitherto it has not been demonstrated that phosphorylation of serine 103 has any impact on transcription mediated by the serum response factor.

Similar to ER81, MK2 expression has been demonstrated to inhibit the activity of E47 (34). However, MK2 phosphorylation sites have not been determined, and it remains to be resolved whether MK2 inhibition of E47 is due to direct phosphorylation of E47. In contrast, the transcription factor CREB is activated upon MK2 phosphorylation on serine 133 (9, 10), which is also the phosphorylation site for cAMP-activated protein kinase A. This indicates that MK2 may exert either positive or negative effects on transcription factors.

Altogether, MK2 may regulate ER81-dependent transcription in a manner dependent as well as independent of serine 191 and serine 216 phosphorylation. Thereby, MK2 may ensure that ER81 and its target genes are repressed in unstimulated cells, and it may attenuate the p38-MAP kinase-mediated stimulation of ER81. Because ER81 is involved in many developmental processes (13, 14), MK2 may be an important modulator of these processes, thereby extending its originally described function as a component of the cellular stress response.

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