Myeloid Elf-1-like Factor, an ETS Transcription Factor, Up-regulates Lysozyme Transcription in Epithelial Cells through Interaction with Promyelocytic Leukemia Protein*

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Interaction with Promyelocytic Leukemia Protein*

Up-regulates Lysozyme Transcription in Epithelial Cells through Myeloid Elf-1-like Factor, an ETS Transcription Factor,

The mammalian cell nucleus contains a large number of specialized nuclear domains or compartments. Each nuclear domain has been reported to vary in size from 0.2 to 1.0 μm in diameter, and a typical mammalian nucleus contains 10–30 of these nuclear bodies (2, 4). Two major components, PML and Sp100, are considered to build the framework of PML nuclear bodies (5). PML was identified as part of a fusion protein with retinoic acid receptor α, resulting from the t(15;17) chromosomal translocation expressed in acute promyelocytic leukemia (6, 7). Sp100 was first characterized as an autoantigen in certain autoimmune disorders (8). Although PML and Sp100 are core components of PML nuclear bodies, numerous proteins, such as p53, SUMO-1, CBP, HDAC, Daxx, pRB, and HIPK2, seem to transiently localize to PML nuclear bodies (4, 9–12). A variety of functions has been suggested for PML nuclear bodies, including tumor suppression and transcriptional regulation through the titration, modification, and compartmentalization of proteins (4, 9).

The ETS transcription factor family has more than 30 members, and a number of these factors have been shown to play roles in important physiological processes, including cellular proliferation, differentiation, development, hematopoiesis, angiogenesis, and transformation (13). ETS proteins have conserved DNA binding domain, which is the ETS domain. This ETS domain binds to specific DNA sequence with a variant core motif GGA, which is known as the ETS binding site (13, 14). It has been shown that protein-protein interaction and post-translational modification regulate DNA binding, subcellular localization, and transcriptional activity of ETS proteins (15–20). However, regulation of ETS proteins through nuclear domains has not been studied extensively.

Myeloid elf-1-like factor (MEF) or Elf4, is an ETS protein composed of 663 amino acids. It is widely distributed in hematopoietic and non-hematopoietic tissues. It was initially found to activate the promoters of hematopoietic growth factor genes, granulocyte macrophage-colony stimulating factor, and interleukin-3 (21). MEF physically and functionally interacts with AML1, a transcription factor that is essential for the development of definitive hematopoiesis, and the activity of MEF is repressed by the AML1-ETO fusion protein, which is specifically found in acute myeloid leukemia with t(8;21) chromosomal translocation (22). Recently, it was also found that MEF is essential for the proper function of natural killer cells as determined from knock-out mice (23). We have previously demonstrated that MEF up-regulates lysozyme gene expression in epithelial cells (24). We also found that MEF is constitutively localized in the nucleus under normal or stress conditions (25).
We attempt to investigate the subnuclear localization of MEF and how this regulates MEF transactivation. We report here that MEF is recruited to the PML NBs and physically interacts with PML to enhance MEF transactivation potential. Our finding shows that this interaction up-regulates MEF-mediated transcription of lysozyme gene.

**EXPERIMENTAL PROCEDURES**

**Plasmids**—The luciferase reporter plasmid pGL2-lysozyme-luc and the expression plasmids pCB6-MEF, pEGFP-MEF full-length; pEGFP-MEF deletion mutants coding for GFP-MEF 1–517 and GFP-MEF 1–347 amino acids; and pM-MEF deletion mutants coding for GAL4-MEF 517-477 and GAL4-MEF 477–35 amino acids were cloned as described previously (24, 25). pcDNA3-Flag-PML was also cloned previously (26), whereas pSG5-Sp100 was kindly provided by Drs. J.-S. Seeler and A. Dejean. To generate VP16-PML fusion protein for mammalian two-hybrid assays, pcDNA3-Flag-PML vector was digested with BamHI and XbaI, and the 2.9-kb PML fragment was ligated into the pACT vector (CheckMate mammalian two-hybrid system, Promega Corp., Madison, WI). For VP16-Sp100 fusion protein, a PCR-generated Sp100 with flanking MluI (5′-end) and EcoRV (3′-end) was amplified from pSG5-Sp100 and ligated into a linearized pACT vector.

**Cell Culture and Transfections**—HeLa cell line was obtained from RIKEN Cell Bank and HFK293 cell line was from the American Type Culture Collection. HeLa cells were cultured in minimum essential medium supplemented with 10% fetal bovine serum (BIOSOURCE International) and HEK293 were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum. Cells were maintained at 37 °C in a humidified atmosphere of 5% CO2 and 95% air. Transient transfections of plasmid DNAs were performed with TransIT-LT-1 (Mirus Corp., Madison, WI) according to the manufacturer’s recommendations. Specifically, 3 μl of TransIT-LT-1 reagent diluted with reduced serum Opti-MEM (Invitrogen) was mixed with total DNA in a ratio of 1:3 (DNA/LT-1) and applied to subconfluent cells in minimum essential medium or Dulbecco’s modified Eagle’s medium with fetal bovine serum.

**Immunofluorescence**—HeLa cells were grown on poly-L-lysine-coated 35-mm glass-bottomed dishes and transfected with the pEGFP-MEF constructs pcDNA3-Flag-PML, pSG5-Sp100, or a combination of these, fixed in 3.7% paraformaldehyde, and permeabilized with 0.5% Triton X-100 in phosphate-buffered saline (PBS) for 15 min at room temperature. Fixed cells were subsequently blocked for 60 min at room temperature with PBS containing 1 mg/ml bovine serum albumin and incubated with a 1:100 dilution of primary antibody/rabbit anti-MEF (Transgenic, Inc., Kumamoto, Japan), mouse anti-PML (Santa Cruz Biotechnology, Santa Cruz, CA), or goat anti-Sp100 (Santa Cruz Biotechnology) for 1 h at room temperature. Cells were washed three times with PBS and then stained with 1:100 dilution of fluorescein isothiocyanate-conjugated anti-rabbit, TRITC-conjugated anti-goat, TRITC-conjugated anti-mouse, or Cy5-conjugated anti-mouse secondary antibody (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA) for 1 h at room temperature. Cells were washed three times with PBS and mounted with Vectashield mounting medium (Vector Laboratories, Burlingame, CA). Immunofluorescence analyses were carried out using Fluoview FV-500 confocal laser scanning microscope (Olympus, Tokyo, Japan).

**Luciferase Assays**—HeLa cells were seeded in 12-well plates. Co-transfection of various plasmids was performed with 0.2 μg of reporter plasmid and the indicated combinations of 0.1 μg of MEF, 0.5 μg of PML, and 1 μg of Sp100 plasmids. Empty vector was added where necessary to ensure a constant amount of input DNA. Each sample was co-transfected with 10 ng of pHR-GK-TK vector (Promega Corp.), which expresses Renilla reniformis luciferase to verify that differences in firefly luciferase reporter gene expression were not caused by differences in transfection efficiency. Twenty-four or forty-eight hours after transfection, the medium was removed and cells were harvested. Luciferase activity was measured using a Dual-Luciferase Reporter Assay system (Promega Corp.) and a luminometer (Turner Designs Luminometer Model TD-2020; Promega Corp.). Absolute light emission generated from the luciferase enzyme reaction was determined. Relative luciferase activity was plotted; it represents the fold induction of activity assayed from experimental transfection with respect to activity associated with basic vector alone. Values are shown as means ± S.E. (n = 3).

**RT-PCR**—HeLa cells were seeded in 6-well plates and transfected with the indicated combinations of 0.25 μg of MEF, 1.25 μg of PML, and 2.5 μg of Sp100 expression plasmids. Empty vector was added where necessary to ensure a constant amount of input DNA. Total RNA was extracted from 1 × 106 cells using Isogen (Nippongene). RT-PCR experiments were performed with an RNA PCR kit (ReverTra; TOYOBO) according to the manufacturer’s instructions. The reverse transcription reaction was carried out at 42 °C for 30 min, 99 °C for 5 min, and 4 °C for 5 min. PCR was carried out at 98 °C for 1 min for 1 cycle, 98 °C for 15 s, 60 °C for 20 s, and 74 °C for 90 s for 15–40 cycles, and 74 °C for 20 min for 1 cycle. The following primers were used for lysozyme: 5′-primer, CTTTCGGAGC-TAGGCACTCTGACCTAGCAGT; 3′-primer, AAAAAATTCTCGAGTTACACTCCAAACCTTGG; for glyceraldehyde-3-phosphate dehydrogenase: 5′-primer, CCGGGAAGCTTGT-CCAGGGATCAG; 3′-primer, GATGCTCAAGTG; for glyceraldehyde-3-phosphate dehydrogenase: 5′-primer, CCGGGAAGCTTGT-CCAGGGATCAG; 3′-primer, GATGCTCAAGTG.

**Immunoprecipitation and Western Blot Analysis**—HeLa and HEK293 cells were grown on 10-cm dishes and HEK293 cells were transfected with 1.5 μg of MEF and 7.5 μg of PML. For immunoprecipitation, 1 × 106 cells were treated with 5 μM dimethyl 3,3′-dithiodiisopropylidimide-2-HCl (Sigma) at 4 °C for 30 min. The cross-linking reaction was terminated by washing the cells with a buffer (150 mM NaCl and 100 mM Tris-HCl, pH 8.0). The treated cells were lysed in lysis buffer.
(150 mM NaCl, 50 mM Tris-HCl, pH 8.0, 5 mM EDTA, 0.5% deoxycholate, and 5% Nonidet P-40). The lysate was diluted to 1:5 by adding a buffer (150 mM NaCl and 50 mM Tris-HCl, pH 8.0) and then mildly sonicated. After centrifuging for 20 min, the supernatant was incubated with appropriate antibodies for 90 min and then with protein G beads (Amersham Biosciences) at 4 °C for 2 h. The beads were washed five times with a buffer (150 mM NaCl, 50 mM Tris-HCl, pH 8.0, and 0.5% Nonidet P-40). Immunoprecipitates were suspended in a Laemmli sample buffer (2% SDS, 100 mM dithiothreitol, 60 mM Tris-HCl, pH 6.8, and 0.001% bromphenol blue). Samples were separated by 7.5% SDS-polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride membranes (Millipore Corp., Bedford, MA). The
membrane was blocked with a solution of PBS containing 0.05% (v/v) Tween 20 and 5% nonfat milk. After three washes in PBS containing 0.05% (v/v) Tween 20, the membrane was incubated for 1 h in a 1:200 dilution of a primary antibody. After another three washes in PBS containing 0.05% (v/v) Tween 20, the membrane was incubated for 1 h with 1:10,000 dilution of the corresponding secondary antibody. The membrane was reacted with chemiluminescence reagent ECL (Ameri-
sham Biosciences) to visualize the blots.

RESULTS

Overexpression of PML But Not Sp100 Induces Accumulation of MEF in PML Nuclear Bodies—To investigate the subnuclear distribution of MEF, we transfected GFP-MEF into HeLa cells in which the endogenous MEF gene was minimally expressed. As shown in Fig. 1A, GFP-MEF distributed itself diffusely throughout the nucleus except in the nucleoli. Simultaneous staining with the endogenous PML proteins showed that MEF only slightly co-localized with PML. Because several proteins interact with PML and are recruited into PML nuclear bodies, resulting in the regulation of their transcriptional activity (27), we examined whether the subnuclear localization of MEF is affected by PML overexpression in HeLa cells. Because several proteins interact with PML and are recruited into PML nuclear bodies, we transfected GFP-MEF into HeLa cells in which the endogenous MEF gene was minimally expressed. As shown in Fig. 1A, GFP-MEF distributed itself diffusely throughout the nucleus except in the nucleoli. Simultaneous staining with the endogenous PML proteins showed that MEF only slightly co-localized with PML. Because several proteins interact with PML and are recruited into PML nuclear bodies, resulting in the regulation of their transcriptional activity (27), we examined whether the subnuclear localization of MEF is affected by PML overexpression in HeLa cells. As shown in Fig. 1A, overexpressed PML induced the accumulation of MEF in PML nuclear bodies. The accumulation of MEF into the PML NBs is therefore specifically mediated by PML. Next, we determined the subnuclear localization of GFP-MEF when both PML and Sp100 were overexpressed. We co-transfected HeLa cells with GFP-MEF, PML, and Sp100 constructs and double-stained them with anti-PML and anti-Sp100 antibodies, which were subsequently immunolabeled with Cy5- and TRITC-conjugated secondary antibodies. Fig. 1B showed that GFP-MEF localized outside of the PML NBs, whereas PML and Sp100 merged within these nuclear bodies. The data suggest that Sp100 overexpression can negatively affect the PML-induced accumulation of MEF in the nuclear bodies.

PML Enhanced the MEF Transactivation of Lysozyme Gene—We next investigated the functional relevance of the accumulation of MEF in PML NBs by examining MEF transcriptional activity. We performed luciferase assay using lysozyme promoter, which is a target gene of MEF. Co-transfection of MEF and PML doubled up-regulated the lysozyme promoter activity (Fig. 2A). Moreover, the endogenous lysozyme gene expression was increased by PML co-transfection as demonstrated by semi-quantitative RT-PCR (Fig. 2B). We also investigated the involvement of Sp100 on the regulation of MEF transactivation. Co-transfection of Sp100 with MEF did not significantly change the localization of MEF, which remained distributed in the nucleoplasm (Fig. 1B). The accumulation of MEF into the PML NBs is therefore specifically mediated by PML. Next, we determined the subnuclear localization of GFP-MEF when both PML and Sp100 were overexpressed. We co-transfected HeLa cells with GFP-MEF, PML, and Sp100 constructs and double-stained them with anti-PML and anti-Sp100 antibodies, which were subsequently immunolabeled with Cy5- and TRITC-conjugated secondary antibodies. Fig. 1C showed that GFP-MEF localized outside of the PML NBs, whereas PML and Sp100 merged within these nuclear bodies. The data suggest that Sp100 overexpression can negatively affect the PML-induced accumulation of MEF in the nuclear bodies.
not significantly enhance MEF transactivation or endogenous lysozyme gene expression (Fig. 2, C and D). These results are consistent with the immunocytochemical data in Fig. 1B demonstrating that Sp100 did not affect MEF localization. However, the PML-enhanced MEF transactivation of the lysozyme promoter was decreased by the overexpression of Sp100 (Fig. 2E). The observable decrease in lysozyme transactivation could possibly have been a result of Sp100 overexpression blocking the translocation of MEF into the PML nuclear bodies (Fig. 1C). Western blots showed that the levels of both endogenous and transfected MEF were not altered by co-transfection of PML and Sp100 (Fig. 2, F–H), excluding the possibility that MEF protein expression levels were involved in the changes of PML-enhanced MEF transactivation of the lysozyme promoter. Collectively, these results suggest that PML positively contributes to the MEF-regulated lysozyme activation.

Physical Interaction between MEF and PML.—We next sought to determine whether MEF and PML interact directly. HeLa cells were transfected with MEF and PML. Immunoprecipitation with anti-PML antibody and subsequent Western blotting with anti-MEF antibody revealed that PML and MEF interacted under overexpressed conditions. This interaction was verified using anti-MEF antibody for immunoprecipitation, whereas anti-PML antibody was used to probe the blotted precipitates (Fig. 3A). To determine whether MEF and PML interaction occurs endogenously, we used the whole cell extracts from HEK293 cells, which highly express MEF. In the same manner, anti-PML and anti-MEF antibodies were used for immunoprecipitation and probing the blotted precipitates. Fig. 3B showed that MEF and PML also interacted at endogenous levels. We immunoprecipitated MEF and Sp100 in HEK293 cells but we could not detect an interaction between these two proteins under endogenous and overexpressed conditions (data not shown).

Mapping the Interaction Domain of MEF.—We next sought to map the region(s) of MEF responsible for interacting with PML by performing the mammalian two-hybrid assay in HeLa cells. We fused various parts of MEF to the DNA binding-domain of the yeast GAL4 protein. PML was fused to the activation-domain of the Herpes simplex virus VP16 protein. The interaction of these fusion proteins was tested in transiently transfected HeLa cells with a reporter construct driven by five GAL4 binding sites linked to luciferase. The result showed that MEF amino acids 477–663 strongly up-regulated the reporter gene together with PML much more than the full-length construct or any regions of MEF (Fig. 4B; data not shown). This implied that the C-terminal portion of MEF interacts with PML. We next sought to determine the region of MEF required for accumulation in PML nuclear bodies. We first examined the subnuclear localization of various GFP-MEF constructs. Immunofluorescence experiments showed that full-length MEF and MEF amino acids 1–517 accumulated in PML nuclear bodies. The shorter construct, MEF amino acids 1–347, failed to colocalize with PML (Fig. 5A). These results suggest that MEF amino acids 348–517 are essential for the translocation of MEF into the PML nuclear bodies. We performed luciferase assay using the lysozyme reporter plasmid to determine the region of MEF required for its transactivation enhanced by PML. Consistent with the immunofluorescence results, full-length MEF and MEF amino acids 1–517 up-regulated lysozyme transcription that was enhanced by PML. PML did not enhance the activity of MEF amino acids 1–347 (Fig. 5B). These data implied that MEF amino acids 348–517 are required not only for accumulation of MEF in PML nuclear bodies but also for the PML-enhanced MEF transactivation of the lysozyme gene.

Heat Shock Stress Induces Accumulation of MEF in PML Nuclear Bodies and Enhanced MEF Transactivation.—Many previous studies showed that diverse cellular stresses, including viral infection, interferon, heat shock, heavy metals, ultraviolet, and oncogenes, alter the subnuclear distribution of PML and PML-associated proteins and affect their function (4, 10, 11, 29, 30). Therefore, we determined whether heat shock altered the subnuclear distribution of MEF and its activity. HeLa cells were transfected with GFP-MEF, and heat-shock treatment was performed at 42 °C for 90 min before fixation or extraction of cells. MEF accumulated in endogenous PML nuclear bodies immediately after heat-shock treatment, and its transactivation was enhanced (Fig. 6, A and B). No change in MEF protein expression was observed after heat-shock treatment (Fig. 6B, right). To determine whether endogenous MEF can localize to PML nuclear bodies after heat shock, we used HEK293 cells, which express more MEF than HeLa cells. HEK293 were stained with MEF and PML antibodies and immunolabeled with fluorescein isothiocyanate- and TRITC-conjugated secondary antibodies. As shown in Fig. 6C, endogenous MEF translocates to endogenous PML nuclear bodies immediately after heat shock. This result can correlate to the up-regulation of the lysozyme promoter observed after heat-shock treatment of HEK293 cells in the reporter assay.
Furthermore, the endogenous lysozyme expression increased after heat-shock treatment as determined by semi-quantitative RT-PCR using HEK293 cells (Fig. 6E). Collectively, these results suggest that the accumulation of MEF in PML nuclear bodies and increase of MEF transactivation potential could be induced in response to heat shock stress.

**DISCUSSION**

We have presented here the evidence that MEF transactivation is enhanced through a direct interaction between MEF and PML. Because MEF is constitutively localized in the nucleus (25), we first proposed that the elucidation of the subnuclear localization of MEF might provide valuable information as to how the MEF activity is regulated. Various transcription factors and co-factors display a diffuse nuclear localization pattern, but if PML is overexpressed, progesterone receptors and co-factors such as TIF1α are partially shifted to the nuclear body through their interaction with PML (31). Transcriptional regulators such as p53 and CBP are also found in the nuclear body (32, 33). It is therefore possible that transcriptional factors are recruited to the PML nuclear bodies either to take part in transcription or to be modified (4). In our immunofluorescence experiments, GFP-MEF was distributed throughout the nucleus but partly accumulated in PML nuclear bodies when PML was overexpressed (Fig. 1A).

Although the physiological functions of PML nuclear bodies remain largely unknown, many studies have suggested that they play a role in the regulation of transcription (4, 34). Our luciferase assay data using the lysozyme reporter showed that the transcriptional activity of MEF was enhanced by PML overexpression. Moreover, we confirmed that MEF transacti-
vation of endogenous lysozyme gene expression was up-regulated by PML in RT-PCR experiments (Fig. 2). Based on the co-localization and functional interaction of MEF and PML, we hypothesized and subsequently demonstrated by immunoprecipitation that these two proteins directly interact in mammalian cells. It has been observed that overexpressed bacterial lac repressor protein localized to the PML body independent of transcription (35); thus, interactions observed when PML and/or the partner protein are overexpressed are not always indicative of a real interaction. We proved that MEF and PML interact endogenously (Fig. 3B), precluding the possibility that the observable interaction was artificial. The mammalian two-hybrid assays of the MEF deletion mutants showed that the physical interaction between MEF and PML involves the MEF amino acids 447–663 (Fig. 4B), a region that contains a proline-rich domain. Moreover, we showed that the residues 348–517 of MEF, but not the N-terminal region from 1–347, are necessary for MEF to co-localize with PML in the nuclear bodies as well as for the PML-enhanced MEF up-regulation of the lysozyme gene (Fig. 5). These results suggest that MEF amino acids 477–517, or the proline rich region of MEF, may be important for its interaction with PML. The amino acid proline is critical among the primary structures of many ligands for protein-protein interactions, and proline-rich sequences are commonly found in situations requiring rapid recruitment or interchange of several proteins (36). The proline-rich homeodomain protein has been reported to bind with the RING domain (the zinc-binding domain) of PML (37). We previously indicated that MEF has two transactivation domains located in the N-terminal region of MEF (1–52), which is a potent transactivation domain, and in the C-terminal region (477–663), which is a weak transactivation domain (25). The present findings that the MEF C-terminal region interacts with PML, which enhances MEF transactivity, could partly explain the activation mediated by the C-terminal region of MEF. We have not yet determined, however, exactly how PML regulates MEF transactivity. It may be possible that MEF is recruited to PML nuclear bodies and undergoes modification such as SUMOylation (which we are currently investigating), resulting in the regulation of MEF transactivation potential.

The reported interaction between the ETS family member ETS-1 and Sp100 (28) has led us to examine whether Sp100 can affect MEF regulation of MEF transactivation potential. Because MEF plays a role not only in innate immunity but also in tumor suppression (41), it will be interesting to further elucidate the involvement of PML nuclear bodies in the tumor suppressive function of MEF.

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