Regulation of Receptor Activator of NF-κB Ligand-induced Tartrate-resistant Acid Phosphatase Gene Expression by PU.1-interacting Protein/Interferon Regulatory Factor-4

SYNERGISM WITH MICROPHTHALMIA TRANSCRIPTION FACTOR*

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The receptor activator of NF-κB ligand induces the expression of tartrate-resistant acid phosphatase (TRAP) and transcription factor, PU.1-interacting protein (Pip), during osteoclastogenesis. In this paper, we have examined the role of transcription factors in the regulation of TRAP gene expression employing reporter constructs containing the promoter region of TRAP gene. Transient transfection of RAW264 cells with sequential 5’-deletions of mouse TRAP gene promoter-luciferase fusion constructs indicated that at least two sites are required for the full promoter activity. Deletion and site-directed mutagenesis studies revealed that M-box and interferon regulatory factor element sites are critical for TRAP gene expression in the cell, suggesting that microphthalmia transcription factor (MITF) and Pip could induce the gene expression independently. Moreover, the overexpression of MITF and Pip functionally stimulated TRAP promoter activity in a synergistic manner. Analysis of the deletion mutants of Pip protein indicated that both N-terminal DNA-binding and C-terminal regulatory domains are indispensable to the promoter-enhancing activity. Subcellular localization of green fluorescence protein-fused Pip and its mutant proteins indicated that the C-terminal domain is required for the translocation of Pip into the nucleus. These results suggest that Pip regulates and acts synergistically with MITF to induce the promoter activity of TRAP gene.

Bone morphogenesis, remodeling, and resorption are controlled in part by osteoclasts. These cells differentiate from hematopoietic myeloid precursors of macrophage/monocyte lineage under the control of osteotropic hormones and local factors produced by supporting cells such as osteoblasts and stromal cells (1–9). The receptor activator of NF-κB ligand (RANKL) (10), also referred to as osteoclast differentiation factor (11), tumor necrosis factor-related activation-induced cytokine (12), or osteoprotegrin ligand (13) is a tumor necrosis factor-like cytokine expressed by stromal cells and is capable of stimulating osteoclast differentiation. Soluble RANKL can induce osteoclastogenesis both in vitro and in the absence of stromal cells in vivo. Moreover, it has been shown that mutant mice with either RANKL or its receptor RANK gene disrupted exhibit severe osteopetrosis and osteoclast defects, indicating that RANKL plays an essential role in osteoclast differentiation (14, 15).

Tartrate-resistant acid phosphatase (TRAP) and cathepsin K are osteoclast marker proteins that are expressed in functionally matured osteoclasts. Disruption of the genes encoding these marker proteins in mice results in osteopetrosis (16, 17), indicating that elucidation of the mechanism of regulation of these genes is important in understanding the mechanism involved in the maturation of osteoclasts and the molecular basis of human disorders associated with defects in osteoclast function. The importance of gene regulation of these proteins in the functional maturation of osteoclasts is also suggested by the fact that osteopetrosis results after knockout in mice of genes encoding transcription factors such as c-Fos, PU.1, or NF-κB (p50 and p52 double knockout mice) (18–21).

In our previous work, we showed that RANKL induced the differentiation of both primary murine bone marrow cells and the murine monocytic cell line, RAW264 cells, into TRAP-positive osteoclast-like multinucleated cells through activation of the p38 mitogen-activated protein kinase signaling pathway (22). It has been shown that mice with the TRAP gene disrupted exhibit mild osteopetrosis, although multinucleated osteoclasts are still observed (16). Recently, it has been reported that microphthalmia transcription factor (MITF) regulates TRAP gene expression (23). It has also been reported that MITF is expressed in osteoclast progenitors and that its presence facilitates osteoclastogenesis (24). In fact, microphthalmia mutant (mil/mil) mice expressing a dominant negative form of MITF exhibit defects in osteoclastogenesis and osteopetrosis (25). However, because osteoclasts obtained from tgf/tgf mice, Mi null mutant mice, are normal (25), it appears that MITF is not essential for osteoclast differentiation and its resorptional function. These results, together with the fact that there are several transcription binding sites in the promoter region of TRAP gene, have prompted us to analyze the mechanisms of TRAP gene expression during RANKL-induced osteoclast differentiation and maturation.

The interferon regulatory factor (IRF) family of transcription factors possesses multifunctional biological activities including...
cell proliferation, differentiation, apoptosis, and antiviral activity (26–29). Among the nine homologues so far identified, PU.1-interacting protein (Pip), also termed IRF-4, lymphoid-specific IRF, or interferon consensus sequence-binding protein in adult T-cell leukemia cell lines or activated T cells (ICSAT), has been shown to be essential for lymphoid cell development (30–33). However, the role of Pip in macrophage remains to be elucidated. Our results reported in this paper indicate for the first time that Pip is increased in osteoclast-like cells that differentiated from RANKL-treated cells of macrophage lineage and can regulate TRAP gene expression. Moreover, Pip and MITF synergistically induce the increase in TRAP gene expression, suggesting that transactivation of both M-box and IRF-E sites is required for maximum induction of the gene expression.

**EXPERIMENTAL PROCEDURES**

*Materials—* Human recombinant soluble RANKL (sRANKL) was purchased from Peprotec EC Ltd. (London, UK). Polyclonal antibody against Pip/IRF-4 was obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Enhanced green fluorescence protein (GFP) expression vector, pEGFP-C1, was purchased from CLONTech (Palo Alto, CA). pSRo human ICSAT (IRF-4) cDNA was kindly provided by Dr. T. Yamagata of University of Tokyo.

*Cell Culture—* The mouse RAW264 cells (RIKEN, RCB0535) were maintained in minimum essential medium supplemented with 5% fetal bovine serum (JRH Biosciences, Lenexa, KS), and 1% non-essential amino acids as described previously (22). After 3 or 5 day, the cells were washed with phosphate-buffered saline and subjected to Western blot analysis. The HEK 293 cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum and 100 μg/ml kanamycin.

*Plasmid Construction—* The pcDNA3FLAG-Pip (FLPip) and pcDNA3 PU.1 plasmids were kind gifts from Dr. H. Sighn (Harvard Medical School). A genomic clone encoding the 5′-flanking region of the gene promoter were amplified by PCR using specific primers and TBX6 as a template. These fragments were then subcloned into the Xhol/HindIII sites of the pGL3 basic vector containing the luciferase reporter gene (Promega, Madison, WI).

*Expression plasmids for the Pip deletion mutant, PipΔN, which lacks the sequence between amino acids 39 and 117 was constructed by digestion of pcDNA3FLAG-Pip with SmaI and EcoRV and then ligated. As for PipΔC lacking amino acids between 378 and 408, the pcDNA3FLAG-Pip vector was digested with HindIII and NheI, and then the fragment containing pcDNA3 vector and the C-terminal region corresponding to amino acid residues 409–451 was obtained. A fragment containing Pip (1–378) and the hemagglutinin tag region was amplified by PCR using T7 primer and a specific primer, 5′-CGGTGCTAGCCGGAATTCCTAAC-3′ (sense), and then digested with NheI and NotI. The FLAG-Pip fragment was inserted into the HindIII and NheI sites of pcDNA3 vector containing the C-terminal region of Pip.**

Detection of mRNA Expression by RT-PCR—Total RNAs for cDNA synthesis were isolated from murine bone marrow and RAW264 cells as described (34). RNA was reverse-transcribed using Superscript II reverse transcriptase (Life Technologies, Inc.), 1 μm dNTPs, 1 μg of oligo(dT) primers, and the supplied buffer. RT-PCR assays were carried out using the following primer pairs for TRAP, Cathepsin K, RANK, 5′-CATGACAAGGAGGTTCCAGGACACT-3′ (sense), 5′-ACAGGTTAGCGGTAGCCCTATGATGTC-3′ (antisense); and Cathepsin K, 5′-TGATGAAA-TCTCTCGGCGT-3′ (sense), 5′-TCATGTCTCCCAAGTGGTTC-3′ (antisense); PCRs for TRAP, RANK, and β-actin were carried out for 1 cycle at 95 °C for 9 min, followed by 25, 30, or 35 cycles at 94 °C for 0.5 min, at 54 °C for 1 min, and at 72 °C for 1 min. mRNA levels were quantified by a software program of imaging analyzer, NIH Image 1.61. The relative amount of the TRAP mRNAs was normalized to that of β-actin mRNA.

Transfection and Luciferase Assay—For transfection of reporter plasmids, RAW264 cells or HEK 293 cells were plated on 12-well plates at a density of 3 × 10⁴ cells/well on the day before transfection. A total of 6.3 μg of plasmid DNA was mixed with Superfect (Qiagen, Santa Clarita, CA) and transfected into the cells following the manufacturer’s protocol. After 48 h of transfection, the cells were washed three times with phosphate-buffered saline and then lysed in reporter lysis buffer (Promega). Luciferase activity was then measured with a luciferase assay system (Promega) according to the manufacturer’s instructions. Luciferase activity was measured in triplicate, averaged, and then normalized to β-galactosidase activity to correct for transfection efficiency. β-Galactosidase activity was measured using a o-nitrophenyl-β-d-galactopyranoside as a substrate.

Western Blot Analysis—Western blot analyses were performed as described previously (37). In brief, the cells were lysed in a lysis buffer (20 mM Hepes-KOH, pH 7.4, 2 mM EGTA, 50 mM β-glycerophosphate, 140 mM NaCl, 20 mM DTT, 2% SDS, 200 μg/ml of leupeptin, 20 μg/ml of aprotinin, and 0.1% sodium deoxycholate). The samples were subjected to Western blot analysis with an antibody against Pip, C-Fos (Stratagene), and α-tubulin (Promega). The relative amount of the protein in Pip-IRF4-double expression and control cells was compared with that of control cells incubated without RANKL but otherwise processed in the same day.
0.1% Triton X-100, 10% glycerol, 1 mM dithiothreitol, 1 μg/ml leupeptin, 5 μg/ml aprotinin, 1 mM phenylmethylsulfonyl fluoride, 1 mM sodium orthovanadate). Whole cell extracts were prepared by centrifugation at 10,000 × g for 15 min at 4 °C. Whole cell extracts (30 μg) were electrophoresed on a 10% SDS-polyacrylamide gel and blotted onto polyvinylidene difluoride membranes. Immunoblot detection was performed with the corresponding goat antiserum using an ECL detection kit (Amer sham Pharmacia Biotech). Quantitative analysis of Pip protein expression level was performed by using a software program of imaging analyzer, NIH Image 1.61.

**Fluorescence Microscopy**—cDNA encoding intact or mutant Pip was ligated in-frame into HindIII/BamHI sites of pEGFP-C1 (pEGFP-Pip, -PipN, or -PipAC). To assess the intracellular localization of GFP fusion proteins, the expression plasmids were transfected into HEK 293 cells. After incubation, the medium was removed and replaced with phosphate-buffered saline. Then the cells were visualized by using a fluorescence microscope equipped with the fluorescein isothiocyanate filter set.

**RESULTS**

**Expression of TRAP Gene by RANKL**—Initially, we examined the effects of RANKL on the expression of osteoclast-specific TRAP mRNA in a murine monocytic cell line, RAW264. Cells. Semiquantitative RT-PCR analysis was performed to estimate the relative expression levels of the TRAP gene. As shown in Fig. 1, incubation of RAW264 cells with RANKL increased the expression level of TRAP mRNA within 3 days. In contrast, RANKL had no significant effect on the expression levels of mRNAs for c-fos, RANK, and β-actin up to 5 days. Densitometric analysis indicated an 8-fold increase in the expression level of TRAP mRNA during the incubation period. Similar results were obtained employing murine bone marrow cells treated with RANKL and macrophage colony-stimulating factor (data not shown). We also analyzed another osteoclast specific gene, cathepsin K, and found that RANKL increased the expression of its mRNA level by 25-fold. These results suggest that RANKL-induced osteoclastogenesis is associated with its ability to induce osteoclast-specific gene expression.

**Induction of Pip Protein by RANKL**—Several potential DNA-binding elements such as AP-1, M-box, PU.1, and IRF-E were detected in the 5′-upstream region of the gene (34–38). Among the transcription factors possibly included in the regulation of TRAP gene, we focused on Pip because it is expressed in macrophages as well as lymphoid cells and can form a complex as well as act synergistically with PU.1 (30, 39). It was shown that the disruption of the PU.1 gene caused the depletion of cells of macrophage/monocyte lineage and induced osteopetrosis in mice, suggesting a critical role for the protein, Pip, in osteoclastogenesis. To examine whether or not RANKL affected the expression level of Pip protein, RAW264 cells were cultured in the presence or absence of RANKL. Although increase in the Pip protein expression level was observed in control cells at day 3, it returned to the basal level at day 5 (Fig. 2A). When compared with control cells, an increase in the expression level was observed in cells treated with RANKL. Quantitative analysis indicated that RANKL caused 2.0- and 8.5-fold increases at days 3 and 5, respectively, indicating that RANKL indeed induced the increase in the expression level of Pip protein. We also examined the effect of RANKL on the expression of other IRF family proteins (i.e., IRF-1, 3, 5, 7). In contrast to Pip/IRF-4, RANKL had little effect on these proteins (data not shown).

**Identification of RANKL Responsive Elements in the TRAP Gene Promoter**—To elucidate the role of Pip in the regulation of TRAP gene expression, chimeric reporter plasmids encoding the luciferase gene and different lengths of the TRAP gene promoter region were constructed and transfected into RAW264 cells. As shown in Fig. 3, RANKL induced the increase in the expression of luciferase activity in cells transfected with either p-1492TRAPLuc or p-1294TRAPLuc. When p-217TRAPLuc was transfected, a decrease in the RANKL-induced enzyme activity was observed. After deletion of the IRF-E site, RANKL exhibited no enhancing activity. These results suggest that at least two factors (i.e., transcription factors binding to M-box and IRF-E sites) are required for the maximum expression of the TRAP gene induced by RANKL.

Because Pip could bind to an IRF-E site (33), promoter-reporter constructs were transfected with or without the Pip expression vector pcDNA3FLAG-Pip, into RAW264 cells (Fig. 4). Upon transfection with each chimeric construct alone, marginal luciferase activity was detected. On the other hand, co-transfection of pcDNA3FLAG-Pip with promoter-reporter constructs that contained the sequence from −217 to +1 of the TRAP gene promoter region (i.e., p-1492TRAPLuc, p-1294TRAPLuc, and p-217TRAPLuc) caused an ~4-fold increase in luciferase activity. No increase in enzyme activity was detected by the co-transfection of pcDNA3FLAG-Pip and p-193TRA-
These results suggest that by binding to the IRF-E site and not the PU.1 site, Pip plays a role in the regulation of TRAP gene expression.

Fig. 5A shows the effects of various transcription factors on the expression of luciferase activity of co-transfected p-1492TRAPLuc plasmid and either Pip or MITF expression plasmid as shown in the figure. After 48 h, luciferase activity was measured as described. Vec., control vector. B, RAW264 cells were co-transfected with 1.0 µg of either Pip or MITF expression plasmid and 1.0 µg of sequentially deleted reporter constructs as shown in the figure. After 48 h, luciferase activity was measured as described. C, functional analysis of the M-box and IRF-E sites of the TRAP gene promoter in RAW264 cells. Left, schematic representation of the constructs used in the transfection assay. Right, intact M-box and IRF-E sites are required for synergistic action. RAW264 cells were co-transfected with a mutant plasmid and Pip and/or MITF expression plasmids as indicated in the figure. After 48 h, luciferase (Luc.) activity was measured as described.

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Fig. 5A shows the effects of various transcription factors on the expression of luciferase activity of co-transfected p-1492TRAPLuc plasmid. Pip protein induced an ~5-fold increase in luciferase activity. MITF, which has been shown to regulate TRAP gene expression by binding to the M-box and IRF-E sites of the TRAP gene promoter in RAW264 cells. Left, schematic representation of the constructs used in the transfection assay. Right, intact M-box and IRF-E sites are required for synergistic action. RAW264 cells were co-transfected with a mutant plasmid and Pip and/or MITF expression plasmids as indicated in the figure. After 48 h, luciferase (Luc.) activity was measured as described.

To identify the promoter region(s) mediating the synergistic action between Pip and MITF, these transcription factors were expressed in RAW264 cells transfected with various chimeric constructs. As shown in Fig. 5B, synergistic action was observed in cells expressing either p-1492TRAPLuc or p-1294TRAPLuc. Cells expressing p-217TRAPLuc, of which the M-box site was deleted, did not show any synergistic action. Because Pip had no effect on the expression of luciferase activ-
Intracellular Functions of Pip and TRAP—To determine the intracellular function of Pip, we first tried electrophoretic mobility shift assay to detect proteins binding to the IRF-E site of the TRAP gene. However, we could not detect any binding activity in nuclear extracts prepared from RAW264 cells treated with or without RANKL (data not shown). In addition, because no anti-Pip antibody affecting the mobility of the complex of Pip and the IRF-E site was available, it was difficult to show the possible involvement of Pip in the regulation of TRAP gene expression by electrophoretic mobility shift assay.

Next, we examined the effects of transcription factors on the expression of the endogenous TRAP gene. Several combinations of plasmids were transfected into HEK 293 cells, and their ability to induce the expression of the gene was examined by RT-PCR. As shown in Fig. 6, although PU.1 had no effect (data not shown), both Pip and MITF could induce an ~2-fold increase in gene expression when transfected with the respective expression plasmid alone. A synergistic increase in the endogenous gene expression was observed in cells co-transfected with pcDNA3FLAG-Pip and pcDNA3.1(-)FLAG-MITF. Co-transfection of these plasmids had no effect on the expression of β-actin. These results indicate that Pip and MITF can indeed act synergistically in vivo and further suggest the critical roles of these two transcription factors in the expression of the osteoclast-specific TRAP gene.

Functional Analysis of Two Domains of Pip Protein—Because Pip protein contains at least two function domains, a DNA-binding domain and a regulatory domain (30), we next constructed expression plasmids for Pip having a deletion in either the DNA-binding domain (PipΔN) or the regulatory domain (PipΔC) to analyze the significance of these two domains (Fig. 7A). As shown in Fig. 7B, whereas intact Pip induced the promoter activity and acted synergistically with MITF, both PipΔN and PipΔC had no effect on the promoter activity, indicating that both DNA-binding and regulatory domains are required for the activity.

To verify the significance of these domains, subcellular localization of Pip and its deletion mutants was analyzed. To visualize proteins, we constructed plasmids expressing GFP-fused Pip or mutant proteins and transfected them into HEK 293 cells. As shown in Fig. 7C, although both GFP-Pip and GFP-PipΔN proteins were found in the nucleus, GFP-PipΔC was localized in the cytoplasm, indicating that the C-terminal regulatory domain is required for the translocation of the protein into the nucleus.

**DISCUSSION**

In the current study, we examined the mechanism of RANKL-induced TRAP gene expression. Our data indicate that transactivations of both IRF-E and M-box sites are critical for RANKL-induced TRAP gene expression. To our knowledge, this is the first observation of the possible involvement of Pip/IRF-4 and its functional interaction with MITF in osteoclast development.

It is well known that TRAP protein is one of the differenti-
The promoter region of TRAP gene contains several transcription factor-binding sites such as AP-1, PU.1, M-box, and IRF-E. Among them, the M-box binding protein, MITF, was shown to regulate TRAP gene expression during osteoclastogenesis. We demonstrated that the sequence ranging from −1294 to −217 is important for RANKL-induced reporter gene expression. Moreover, mutation of the M-box site caused the loss of MITF-mediated reporter gene expression, thereby confirming the role of MITF in the expression of the TRAP gene during osteoclastogenesis (23). More importantly, we found that Pip also induced TRAP gene expression and acted synergistically with MITF. Pip belongs to the IRF family and can bind to the IRF-E site in the promoter region of TRAP gene. We showed that the expression of Pip protein but not of other IRF family proteins was increased after treatment with RANKL, indicating that Pip might be responsible for the enhancement of TRAP gene expression in RAW264 cells. Deletion and mutation analyses of reporter constructs revealed that the intact IRF-E site located in the sequence ranging from −217 to −193 was critical for the activity of Pip protein, demonstrating for the first time that transactivation of the IRF-E site was also important for TRAP gene expression. However, at present, we cannot completely exclude the possibility that other Pip-related IRF-E-binding transcription factors also play roles in the regulation of TRAP gene expression. In this context, HEK 293 cells co-transfected with pcDNA3FLAG-Pip and pcDNA3.1(−)FLAG-MITF show a synergistic increase in the expression of endogenous TRAP mRNA level, supporting the notion that Pip can indeed act synergistically with MITF in vivo.

It was shown that mice lacking PU.1 are depleted of cells of the macrophage/monocyte lineage and exhibit osteoporosis, indicating that PU.1 also plays a critical role in osteoclast development (19). Because the formation of complexes of Pip and PU.1 has been reported (30, 42), it is possible that Pip induces TRAP gene expression via the PU.1 site by interacting with PU.1. However, this is unlikely because mutation of the IRF-E site causes total loss of Pip activity. Moreover, although the association of Pip with PU.1 was detected by immunoprecipitation in RAW264 cells co-transfected with pcDNA3FLAG-Pip and pcDNA3PU.1, no enhancement of the reporter gene expression was observed when compared with cells transfected with pcDNA3FLAG-Pip alone (data not shown). In fact, PU.1 had no effect on the expression of endogenous TRAP mRNA in HEK 293 cells.

Taken together, our results strongly suggest that the transactivation of both M-box and IRF-E sites mediates the synergistic enhancement of TRAP gene expression. RANKL-mediated TRAP gene expression may involve to some extent the up-regulation of Pip protein expression.

Pip contains at least two functional domains, namely, the N-terminal DNA-binding and C-terminal regulatory domains (30). Pip binds to the IRF-E site through the DNA-binding domain and functions as a transcription factor. As expected, disruption of this DNA-binding domain led to the loss of transcription-enhancing activity. It has been reported that a predicted α-helix structure in the C-terminal region of Pip is dispensable to its transcription-enhancing activity (30). This structure has been speculated to be important for interactions with other proteins. We have confirmed the importance of this structure by deletion of the C-terminal amino acid sequence from 395 to 413. To further elucidate the role of this structure in the transcription-enhancing activity, the subcellular localization of Pip and its deletion mutants was examined. Our results indicated that the α-helical structure in the C-terminus of Pip is dispensable to its nuclear localization. Without this structure, Pip would be localized in cytosol and therefore could not function as a transcription factor. At present, we speculate that this structure plays the role of interacting with another protein that is responsible for the nuclear transport of the transcription factor. Further work including the identification of the amino acid sequence necessary for the transport of this protein to the nucleus is required to elucidate the mechanism.

The disruption of the TRAP gene in mice results in mild osteoporosis, but multinucleated osteoclasts are still observed in these mutant mice (16). Thus, it is likely that TRAP is required for the functional maturation of osteoclasts. Identification of the roles of Pip and MITF in the expression of the TRAP gene may help in understanding the molecular basis of human disorders such as osteoporosis in postmenopausal women or the osteolytic bone destruction and hypercalcaemia that occur in patients with multiple myeloma.

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