A Cofactor of tRNA Synthetase, p43, Is Secreted to Up-regulate Proinflammatory Genes*

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An auxiliary factor of mammalian multi-aminoacyl-tRNA synthetases, p43, is thought to be a precursor of endothelial monocyte-activating polypeptide II (EMAP II) that triggers proinflammation in leukocytes and macrophages. In the present work, however, we have shown that p43 itself is specifically secreted from intact mammalian cells, while EMAP II is released only when the cells are disrupted. Secretion of p43 was also observed when its expression was increased. These results suggest that p43 itself should be a real cytokine secreted by an active mechanism. To determine the cytokine activity and active domain of p43, we investigated tumor necrosis factor (TNF) and interleukin-8 (IL-8) production from human monocytic THP-1 cells treated with various p43 deletion mutants. The full length of p43 showed higher cytokine activity than EMAP II, further supporting p43 as the active cytokine. p43 was also shown to activate MAPKs and NFκB, and to induce cytokines and chemokines such as TNF, IL-8, MCP-1, MIP-1α, MIP-1β, IL-1β, and RANTES. Interestingly, the high level of p43 was observed in the foam cells of atherosclerotic lesions. Therefore, p43 could be a novel mediator of atherosclerosis development as well as other inflammation-related diseases.

Cells undergoing programmed cell death (apoptosis) are rapidly removed by monocyte-derived macrophages, suggesting that apoptotic cells might secrete factors with leukocyte and monocyte chemotaxis activity. Endothelial monocyte-activating polypeptide II (EMAP II)† could be a good candidate to be a chemokine recruiting leukocytes and monocytes to cells undergoing apoptosis, because it is released from apoptotic cells and has chemokine activity (1, 2). It has also emerged as a proinflammatory mediator that induces the expression of tissue factor, tumor necrosis factor (TNF), and interleukin-8 (IL-8) in mononuclear phagocytes and polymorphonuclear leukocytes. In addition, EMAP II mRNA is most abundant at sites of tissue undergoing apoptosis in mouse embryo (3). The tissue expressing a high level of EMAP II mRNA also accumulates macrophages, suggesting that EMAP II is a chemoattractant recruiting macrophages into dead cells.

EMAP II was initially purified from the culture medium of murine methylcholanthrene A-induced fibrosarcoma cells based on its capacity to induce activation of tissue factor in human umbilical vein endothelial cells (HUVECs) (1). Since EMAP II is identical to the COOH-terminal domain of the p43 subunit of the mammalian multi-ARN-tRNA synthetase (ARS) complex (4), p43 has been suggested to be a pro-EMAP II. It is cleaved at the amino acid motif ASPT by caspase-7 activated in apoptotic cells (5), producing EMAP II that is sequentially released from the cells.

p43 is a noncatalytic subunit of the mammalian multi-ARS complex (6). Since p43 occupies a central position within the complex in the electron microscopic images of immunocomplexes (7), it could be a scaffolding protein forming the multi-ARS complex. It has been demonstrated that p43 interacts with the NH2-terminal extension of human cytoplasmic arginyl-tRNA synthetase through its NH2-terminal domain (8). Although its COOH-terminal domain is equivalent to EMAP II, this domain contains a tRNA binding motif (9), to deliver tRNAs to the bound arginyl-tRNA synthetase (8).

Although p43 is universally expressed (10), its expression level is variably expressed temporally and spatially in developing mouse (11). For instance, there is a significant surge in the expression of p43 within the lungs on postnatal days 8–16 of mouse. p43 is produced throughout the lung, with predominance in the myoepithelium that lines the bronchioles. In addition, p43 is highly expressed in microglial cells within lesions of experimental autoimmune encephalomyelitis, neuritis, and uveitis (12). The high expression level of p43 in specific developmental stages and tissues suggests that p43 could have unexpected functions in angiogenesis, inflammation, and apoptosis (13).

Mature EMAP II is generated and secreted during late apoptosis (3, 14) so that rapid recruitment of monocytes and macrophages to apoptotic cells could not be explained by EMAP II generation. Since the full-length p43 is constitutively secreted from various cells (3, 15), we focus on the cytokine function of p43. Here, we show that p43 itself was selectively secreted from cells, even in the absence of an apoptosis signal, and had a cytokine function, inducing MIP-1α and MCP-1 as well as TNF and IL-8 from THP-1 cells. Interestingly, p43 was
highly expressed by the foam cells of atherosclerosis lesions, implying that p43 could be a major contributor of inflammation in atherosclerosis development.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Materials—**Human monocyte THP-1 cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum and 50 μg/ml streptomycin and penicillin in a 5% CO2 incubator at 37 °C. 32D mouse myeloid precursor cells were maintained in RPMI 1640 containing 10% fetal bovine serum and interleukin-3 (1 ng/ml). Human embryonic kidney 293 cells were grown in Dulbecco’s modified Eagle’s medium. Preparation of anti-p43 antibody was described previously (8). For the preparation of anti-p18 antibody, the cDNAs encoding the full length of human p18 was amplified by PCR. The resulting PCR product was cloned into a PET28a vector (Novagen) using EcoRI and SalI sites to express as a His-tagged fusion protein. p18 was expressed as an insoluble protein that was used for preparing monoclonal mouse anti-p18 antibody that was made by Boehrte. Anti-Myc and -tubulin antibodies were purchased from Santa Cruz and Sigma, respectively.

**Construction and Purification of p43 Deletions—**The constructs of p43-(1–312), p43-(1–147), and p43-(145–312) were described previously (8). To construct p43-(1–108), PET28a (Novagen) containing the full-length p43 was digested with AgpT18 and SalI, and the large fragment was cloned into an embryonic kidney 293 cells vector to fill up the DNA ends and re-ligated. The DNA fragments coding for p43-(91–256), p43-(91–312), p43-(218–312), and p43-(257–312) regions were synthesized by PCR with specific primer sets (the primer sequences will be available upon request). The specific PCR products were digested with EcoRI and XhoI and ligated into pET28a cut with the same enzymes.

Each of the full-length p43 and p43-deleted constructs was expressed as His-tag fusion protein in Escherichia coli BL21 (DE3) and purified by nickel affinity chromatography and Mono Q or S ion-exchange chromatography as described previously (8). To remove lipopolysaccharide, the protein solution was dialyzed in pyrogen-free buffer (10 mM potassium phosphate buffer, pH 6.0, 100 mM NaCl). After dialysis, the protein was loaded to polyoxymin resin (Bio-Rad) pre-equilibrated with the same buffer, incubated for 20 min, and eluted. The concentration of the residual lipopolysaccharide (LPS) was below 20 pg/ml when determined using the Limulus Amebocyte Lysate QCL-1000 kit (BioWhittaker).

**DNA Transfection—**100-mm dishes of 293 cells were transfected with 5 μl of the indicated Myc-FLAG-tagged pcDNA3-p43 plasmid using Geneporter (Gene Therapy Systems) according to the manufacturer’s protocol. Twenty-four hours after transfection, cell supernatant was collected and concentrated by using Vivaspin (VivaScience). Cells were lysed by sequential treatment with specific antibodies, horseradish peroxidase, and 2% sodium deoxycholate, 0.1% SDS, and 0.1 mM phenylmethylsulfonyl fluoride) containing protease inhibitor mixture (Roche Molecular Biochemicals). The lysates protein and cell supernatants were analyzed by immunoblotting.

**Electrophoresis and Immunoblotting—**THP-1 cells treated with p43 were harvested by centrifugation at 900 × g for 5 min, washed twice with cold phosphate-buffered saline, and lysed with lysis buffer (25 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1 mM EDTA, and 1% Triton X-100) containing 1 mM phenylmethylsulfonyl fluoride and protease inhibitor mixture (Roche Molecular Biochemicals). The lysates protein and cell supernatants were analyzed by immunoblotting.

**Immunohistochemistry—**For immunohistochemical analysis, cardiot endoarterectomy specimens were obtained from 13 patients, aged from 63 to 81, who underwent the surgery at Samsung Seoul Hospital. Atherosclerotic plaque specimens were washed with saline and embedded in optimal cutting temperature to make frozen sections. Standard 5-mm sections were stained using the Labeled Streptavidin Biotin kit (Dako) according to the manual provided by the manufacturer. Monoclonal antibodies to CD68 (KP1), and SMC α-actin (1A4) were purchased from Dako (Glostrup, Denmark). For the detection of p43, rabbit polyclonal antibody raised against recombinant p43 was used in 1 ng/ml concentration.

**RESULTS**

**Full length of p43 Is Constitutively Secreted without an Apoptosis Signal—**Since EMAP II was secreted during late apoptosis, it may not play an active role in recruiting and activating monocytes and macrophages to scavenge apoptotic corpses in the early stage of apoptosis. Although methylcholanthrene A fibrosarcoma cells secrete 40- and 23-kDa (EMAP II) cytokines that stimulate the generation of tissue factor in HUVECs (1), only 23-kDa (EMAP II) protein has been investigated as a cytokine. In addition, the full-length p43 (precursor of EMAP II) is constitutively secreted in methylcholanthrene fibrosarcoma cells, 32D myeloid precursor cells, and human prostatic adenocarcinoma cells even in the absence of apoptotic stimulus (3, 15). All of these previous data suggest that p43 itself could function as a cytokine.

To explore the possibility of p43 as a cytokine, we first investigated the secretion pattern of p43 and EMAP II from normal or apoptotic cells. We incubated 32D myeloid precursor cells with serum-free medium for the indicated times in the presence or absence of IL-3. Since IL-3 withdrawal makes the cells undergo apoptosis within 12 h, we could test the secretion of p43 and EMAP II stimulated by apoptosis. Immunoblotting with anti-p43 antibody revealed that p43 was secreted from the cells as early as 30 min after serum starvation even in the presence of IL-3 (Fig. 1A). The p43 secretion was very specific, because there was no tubulin (a cytoplasmic protein) and p18 (another noncatalytic component of eIF-4F complex) from the median at early time points of IL-3 withdrawal and at any time points in the presence of IL-3. Meanwhile, EMAP II was observed from the cell supernatant only when cells were exposed to apoptosis by IL-3 withdrawal. It was detected in the supernatant at the later time points when p18 and tubulin were also found in the medium (Fig. 1A), implying that EMAP II secretion results from the cellular breakdown by apoptosis.

To confirm these data, we investigated whether excess p43 is...
specifically secreted from 293 cells that do not normally release p43 and EMAP II (data not shown). We transiently overexpressed the Myc-tagged full-length (p43-F), NH2-terminal domain (p43-N) or the EMAP II domain of p43 (EMAP II) (Fig. 1B) in 293 cells. Twenty hours after transfection, the cells were serum-starved for 1, 3, or 5 h. Proteins from whole cell lysate (WCL) and media were analyzed by immunoblotting with anti-Myc antibody. As shown in Fig. 1C, increasing amount of p43-F and -N appeared in the medium, while EMAP II was barely detected even though p43-F, p43-N, and EMAP II are equally overexpressed (left panel indicated as WCL). Since the Myc-tagged p43-F was targeted to the multi-ARS complex (data not shown), it is clearly functional as endogenous p43. From these data, we conclude that p43-F and -N could be secreted from cells in the absence of apoptosis signal if their expression is induced.

Cytokine Domain Analysis—To determine which regions of p43 are involved in its cytokine function, several deletion derivatives of p43 were constructed. The mutant p43 constructs used in this study are shown schematically in Fig. 2A. The mutant proteins were purified as histidine-tagged fusion proteins using a bacterial expression system, and the purified proteins were analyzed by SDS-polyacrylamide gel electrophoresis (Fig. 2B). Endotoxin from the purified proteins was removed by using a polymyxin affinity column. To investigate TNF and IL-8 production by p43 mutant proteins, the purified recombinant proteins were added to THP-1 cells. Two hours after incubation, we determined TNF and IL-8 production by ELISA using their specific antibodies. Since p43-(1–312), p43-(1–146), p43-(1–108), and p43-(92–256) showed higher cytokine activity than p43-(147–312) called EMAP II, the NH2-terminal domain of p43, especially p43-(92–146), might be a stronger cytokine domain than EMAP II. Meanwhile, p43-(218–312) and p43-(257–312) did not activate TNF and IL-8 production. The results corresponded with previous work (16), suggesting that the EMAP II-derived COOH-terminal domain is not necessary for cytokine activity.

p43 Activates MAPKs and NFkB—Activation of MAPKs and NFkB are essential steps for the up-regulation of many proinflammatory cytokines in human monocytes, implying that p43 could regulate the activation of some signal transduction pathways. To address this question, we tested whether p43 affects the activities of the major signaling molecules such as MAPKs and NFkB. Among MAPKs, the activation of ERK1/2 or p38 MAPK was determined by their phosphorylation, and the activity of JNK was determined by the phosphorylation of its substrate, c-Jun. The three tested MAPKs were all activated by p43 in a time- and dose-dependent manner (Fig. 3). Although three different MAPKs showed similar time courses of activation by p43, they showed different sensitivities to the concentration of p43. The activation of ERK1/2 was observed from 1 nm p43, while p38 MAPK and JNK were activated at higher concentrations of p43 (Fig. 3), suggesting that these MAPKs are activated by different mechanisms.

We then tested whether NFkB is also activated by p43. The
The activity of NF-κB was determined by degradation of IκB that suppresses NF-κB (17). The level of IκB was decreased by the treatment of p43 in a time-dependent manner and also from 1 nM p43 (Fig. 3), suggesting that p43 would also activate NF-κB. The activation of NF-κB by p43 was also confirmed by electrophoresis mobility shift assay with an oligonucleotide containing a NF-κB binding site (data not shown). Since the NH₂-terminal peptide of p43 and EMAP II showed the same pattern with p43 in the activation of the tested signaling molecules (data not shown), p43 and EMAP II might share the receptor for activating the signaling pathways.

p43 Activates the Production of Proinflammatory Chemokines—Since p43 activates three different MAPKs and NF-κB, it is tempting to speculate that p43 could activate various genes including those for inflammatory cytokines and chemokines. To characterize changes in mRNA expression of the human monocyte in response to p43, THP1 cells were treated with p43, and total mRNA was extracted at various time points after the treatment. Radiolabeled cDNA was prepared from mRNA by reverse transcription and hybridized to the membrane that carries nonoverlapping arrays of cDNAs for a range of known human genes. The amounts of radioactive probes specifically bound to the cDNA array were analyzed by densitometry, and relative increases in mRNA levels in the p43-treated cells were calculated.

Stimulation of THP-1 cells with the full-length p43 resulted in activation of over 37 genes, out of 1,176 genes tested. As shown in the upper right panel of Fig. 4, TNF is greatly upregulated in p43-treated cells (30-fold increase over the control), consistent with the result of ELISA (Fig. 2C). Even though we used the cDNA array containing 1,176 genes involving in oncogenesis, signal transduction, cell cycle, apoptosis, transcription factors, receptors, cytokines, and chemokines, we found that only 37 genes (mostly cytokine, chemokine, and receptor genes) were highly activated (more than 3-fold increase over control) (Fig. 5), indicating that p43 induces the expression of specific cytokine, chemokine, and receptor genes.

Cytokine and chemokine genes were the most highly induced genes by p43 stimulation (Fig. 4, lower right panel, and Fig. 5). For example, TNF, MCP-1, MIP-1α, MIP-1β, IL-1β, IL-8, MIP-2a, and MIP-1β were very strongly activated 6 h after the p43 treatment (more than 7-fold increase over the control). Since p43 began to activate these genes as early as 30 min after the treatment, these molecules would be directly induced by p43. Some receptor genes such as IL-7R, ErbB-3R, ephrin receptor,

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ERF1, IRF-7, c-Jun, and c-Myc are also activated. Since c-Jun and c-Myc mRNA induction requires JNK activation, JNK activation by p43 (Fig. 3) could explain why c-Jun and c-Myc induction occurs as early as 30 min after the p43 treatment. Moreover, the mRNA level of the adhesion molecule, ICAM-1, was increased after the p43 treatment (11-fold increase at the time point of 2 h). This result is consistent with the previous report on the cell-cell adhesion induced by p43 (2).

To verify the results obtained with the cDNA array, we used ELISA to quantify the amounts of MCP-1 and MIP-1α. THP-1 cells were treated with p43 (100 nM) for 3 h, and the concentration of MCP-1 and MIP-1α was measured from cellular supernatant. As shown in Fig. 6, p43 induced secretion of MCP-1 and MIP-1α, consistent with the cDNA array data (Figs. 4 and 5).

High Amount of p43 Is Detected in the Foam Cells of Atherosclerosis Lesions—The above data raise the intriguing possibility that p43 could be involved in the process of inflammation, since cytokines and chemokines such as TNF, MCP-1, MIP-1α, IL-1β, and IL-8 are found in inflammation areas. A pivotal question, then, is whether p43 is actually expressed in such lesions. We thus examined the level of p43 protein in atherosclerotic lesions by immunohistochemistry using sections of aorta from a human patient car-}

![Fig. 6. Induction of MCP-1 and MIP-1 by p43. THP-1 cells were washed twice with serum-free medium and treated with 100 nM p43 for 6 h. MCP-1 and MIP-1 from medium were determined by ELISA using their specific antibodies. The assay was repeated three times and the averages were shown.](http://www.jbc.org/)

![Fig. 7. High amount of p43 is present in the foam cells of atherosclerosis lesions. A, foam cell (upper panel) or smooth muscle cell-rich area (lower panel) in the neo-intima is shown (× 400), p43 was localized by immunohistochemistry using anti-p43 antibody. Foam cells and smooth muscle cells were identified with immunohistochemistry using anti-CD68 and anti-α-actin antibodies, respectively. The localization of HLA-DR indicates that the foam cells are in an activated state. B, immunoblot analysis of p43 expression in atherosclerotic plaques. Different regions of atherosclerotic plaques were used to prepare the protein extract, and 20 μg of each of the preparations was used for immunoblot analysis with anti-p43 antibody. Lane 1 represents protein extract derived from a fibrous plaque containing dominant smooth muscle cells with a thick fibrous cap. Lane 2 represents protein extract from an atheromatous plaque with heavy infiltration of foam cells and a thin fibrous cap.](http://www.jbc.org/)
throughout postnatal life with the exception of a surge at postnatal days 8–16 (11). In addition, p43 mRNA and protein are localized to the epithelium, with its highest expression in neurons, blood vessels, and at sites of epithelial-mesenchymal interaction (18). Interestingly, p43 is up-regulated in the differentiation stage of hematopoietic stem cells (19). When p43 was highly expressed in 293 cells by transient transfection, it was secreted from the cells that did not release p43 in normal condition (Fig. 1B). This implies that p43 itself could be secreted from cells in which p43 is up-regulated. It would be interesting to understand the signal that induces the expression of p43.

Although p43 was found to be released from cells previously, its ability to function as a proinflammatory cytokine has been neglected. Neglecting mapping of EMA II identified that the NH2-terminal heptamer peptide is responsible for the cytokine activity (16). However, the data in the present work shows that the full-length and NH2-terminal peptide of p43 are more active in the production of proinflammatory cytokines than EMA II (Fig. 2). Thus, the suggested peptide of EMA II does not seem to be the only portion responsible for the cytokine activity.

The full-length p43 has one known function helping aminoacylation of the bound ARSs within cell and another function as a cytokine. There are several other proteins with different functions depending on their cellular localization (20). For example, phosphoglucose isomerase, thymidine phosphorylase, and Hsp70 function as metabolic enzymes or chaperoning protein within cells, whereas they work as cytokines when secreted from cells (20, 21). Like these proteins, p43 lacks a signal peptide necessary for membrane translocation, and the molecules may be secreted without any processing.

Based on the results of this work, the proteolytic cleavage of p43 does not appear to be the prerequisite to generate an active cytokine. This is in contrast to the case of human tyrosyl-tRNA synthetase (22). This enzyme is released from apoptotic cells and split into two distinct cytokines with elastase. However, tyrosyl-tRNA synthetase itself did not show the cytokine activities, indicating that the proteolysis is required to activate each cytokine. If the proteolysis of p43 is not required to activate or release EMA II, its physiological reason remains unclear. We have shown previously that the intact p43 is required for its stimulatory effect on the bound arginyl-tRNA synthetase (8). Therefore, the suggested peptide of EMAP II does not seem to be a cytokine. There are several other proteins with different functions depending on their cellular localization (20). For example, phosphoglucose isomerase, thymidine phosphorylase, and Hsp70 function as metabolic enzymes or chaperoning protein within cells, whereas they work as cytokines when secreted from cells (20, 21). Like these proteins, p43 lacks a signal peptide necessary for membrane translocation, and the molecules may be secreted without any processing.

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