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PARP-1 regulates the expression of caspase-11

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ABSTRACT

Poly(ADP-ribose) polymerase-1 (PARP-1) is a multifunctional enzyme that regulates DNA repair, cell death and transcription of inflammatory proteins. In the present study, we present evidence that PARP-1 regulates the expression of caspase-11 following lipopolysaccharide (LPS) stimulation. Knockdown of PARP-1 suppressed the LPS-induced expression of caspase-11 at both mRNA and protein levels as well as caspase-11 promoter activity. Importantly, PARP-1 was recruited to the caspase-11 promoter region containing predicted nuclear factor (NF)-κB-binding sites when examined by chromatin immunoprecipitation assay. However, knockdown of PARP-1 did not suppress the expression of caspase-11 induced by interferon-γ that activates signal transducer and activator of transcription 1 but not NF-κB. PARP-1 enzymatic activity was not required for the caspase-11 upregulation since pharmacological inhibitors of PARP-1 did not suppress the induction of caspase-11. Our results suggest that PARP-1, as a transcriptional cofactor for NF-κB, regulates the induction of caspase-11 at a transcriptional level.

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1. Introduction

Caspase-11, a murine caspase of the caspase-1 subfamily of cysteine proteases, plays an important role in the regulation of inflammation and apoptosis [1–3]. The expression of caspase-11 is barely detectable under normal condition but highly inducible by pro inflammatory or cytotoxic stimuli [1,2]. Following induction, caspase-11 can regulate inflammatory responses by activating caspase-1 and thereby producing mature interleukin (IL)-1β or IL-18 [2,3]. In addition, it can directly activate caspase-3 to regulate apoptosis [1]. A critical involvement of caspase-11 has been reported in many disease models accompanying pathological apoptosis and inflammation such as brain ischemia, LPS-induced septic shock, experimental autoimmune encephalomyelitis, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease, and spinal cord injury in mice [1,2,4–6]. Therefore, clear understanding of the induction mechanism of caspase-11 is necessary to develop therapeutic strategy targeting caspase-11 induction.

It was reported that proinflammatory stimulators like LPS and interferon-γ (IFN-γ) induce the expression of caspase-11 by activating nuclear factor (NF)-κB and signal transducer and activator of transcription 1 (STAT1), respectively [7]. The signaling pathway leading to caspase-11 induction has been most studied in the LPS-stimulation model. It was shown that LPS-activated toll-like receptor 4 produces reactive oxygen species via interaction with NADPH oxidase complex, which activates mitogen-activated kinase (MAPK) signaling involving apoptosis signal-regulating kinase 1, p38 MAPK or c-Jun N-terminal kinase and ultimately NF-κB to activate caspase-11 promoter [7–10].

Recently, PARP-1 has been shown to function as a transcriptional coactivator of NF-κB and regulates the expression of several proinflammatory genes such as tumor necrosis factor (TNF)-α, IFN-γ and inducible nitric oxide synthase (iNOS) [11–13]. Therefore, it is plausible that caspase-11 whose expression is under the control of NF-κB is also regulated by PARP-1 for its induction. In the present study, we show evidence that the induction of caspase-11 is indeed regulated by PARP-1. Knockdown of PARP-1 suppressed the expression and promoter activity of caspase-11 following LPS stimulation. Moreover, PARP-1 was chromatin-immunoprecipitated on the caspase-11 promoter region containing NF-κB-binding sites. The involvement of PARP-1 in the induction of caspase-11 seemed to be independent of its enzymatic activity and specific for the NF-κB- but not STAT1-activating stimuli. Our results suggest that PARP-1 functions as a coactivator of NF-κB to induce caspase-11 in response to LPS stimulation.

2. Materials and methods

2.1. Mouse embryonic fibroblast cultures

Following removal of head, limbs, and internal organs from 14d gestation mouse embryos, the remaining tissues were minced and

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dissociated by trypsinization and trituration with 0.1% of trypsin–EDTA (JBI). The dissociated cells were resuspended in Dulbecco's modified Eagle's medium (DMEM; JBI) supplemented with 10% fetal bovine serum (FBS; JBI) and 1% penicillin/streptomycin and anti-mycotics solution (JBI). Mouse embryonic fibroblasts (MEFs) were maintained at 37 °C in the 5% CO_2 incubator. The medium was changed every third day.

2.2. RNA interference of PARP-1 and transfection

Expression of PARP-1 was knocked-down using lentiviral PARP-1 short-hairpin RNA (shRNA) constructs created in pLKO.1 vector system (Open biosystems). Transient expression of each vector (3 μg of DNA/35 mm dish) in MEFs was accomplished with TransIT-LT1 transfection reagent according to the manufacturer's protocol (Mirus). After overnight incubation with the transfection reagents, the medium was changed with fresh growth medium. Among 5 different vectors for different target sequences of PARP-1, two (#1 and #4) were confirmed to have maximal knockdown effect upon immunoblot assay. The hairpin sequence for #1 is CGG GAC GAA CTC CTA TTA CAA ATA GTG AAG CCA CAG ATG TAT TTG TAA TAG GAG TTC GTC CCT and for #4 is CCT CGA AAA ACT TCA CAA AGT ATA GTG AAG CCA CAG ATG TAT ACT TTG TGA AGT TTT TCG AGT. pLKO.1 for control shRNA was also purchased from Open biosystems.

2.3. Immunoblot assay

The attached cells were washed three times with ice-cold phosphate-buffered saline and harvested with lysis buffer (150 mM NaCl, 50 mM Tris–HCl pH 8.0, 1% Nonidet P-40, 0.5% Sodium deoxycholate, 0.1% SDS). Protein concentration of the sample was determined by Bradford assay (Pierce). An equal volume of 2× SDS sample buffer (0.25 M Tris–HCl, pH 6.8, 2% SDS, 10% 2-mercaptoethanol, 30% glycerol, and 0.01% bromophenol blue) was added and the sample was heated at 95 °C for 5 min. Protein samples were then separated by 12% SDS–polyacrylamide gel electrophoresis and transferred onto Immobilon-P membrane (Millipore). The membrane was incubated with blocking solution containing 5% skim milk in Tris-buffered saline with Tween 20 (TBST; 50 mM Tris, pH 7.5, 150 mM NaCl, 0.05% Tween 20) for 1 h at room temperature. The membrane was then incubated with primary antibody in blocking solution at 4 °C overnight. After washing three times with TBST for 10 min each, the membrane was incubated with horse radish peroxidase-conjugated anti-rat or anti-mouse IgG (Sigma) for 40 min at room temperature. After washing three times, immunodetection was performed using an ECL kit (Amersham Biosciences) according to the protocol provided by the manufacturer.

2.4. Semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis

Total RNA from cultured cells was prepared using RNeasy mini-kit (Qiagen). cDNA was synthesized using the Moloney Murine Leukemia Virus Reverse Transcriptase (Promega) according to the manufacturer's protocol. The primers used for PCR are as follows: for N-terminal of caspase-11, 5′-AGA AGT CTT ACG GAG TAC C-3′ (forward) and 5′-TGG TGT TCT GAG AGT GCA GC-3′ (reverse); and for mouse β-actin, 5′-GTA TGG AAT CCT GTG GCA TC-3′ (forward) and 5′-AAG CAC TTG CGG TGC ACG AT-3′ (reverse). PCR consisted of an initial denaturation cycle at 94 °C for 2 min, followed by the 26 cycles at 94 °C for 1 min, annealing at 52 or 54 °C for 1 min, and elongation at 72 °C for 1 min. An additional cycle at 72 °C for 5 min completed the amplification process. The number of reaction cycle was determined in the linear working range by performing 5 reactions of different cycle numbers. Amplified PCR products were separated by 2% agarose gel electrophoresis and visualized by ethidium bromide staining.

2.5. Caspase-11 promoter assay

To measure caspase-11 promoter activity, MEFs were transfected with pGL3-caspase-11 promoter and control pRL-TK plasmids and incubated for 36 h. Following drug treatment, dual luciferase activity assay was performed using dual luciferase reporter assay kit (Promega) according to the manufacturer's protocol. pGL3-caspase-11 promoter construct was a generous gift from Dr. R. Beyaert (Ghent University, Belgium) and pRL-TK used as an internal control was purchased from Promega.

2.6. Chromatin immunoprecipitation assay

Chromatin immunoprecipitation (ChiP) was performed using EZ-ChiP kit (Millipore) according to the manufacturer's protocol. Polyclonal anti-PARP-1 antibody was purchased from Abcam (ab6079). The primer pair for the PCR was chosen from the caspase-11 promoter spanning three reported NF-κB binding sites [7]. Forward; 5′-TGC AGC CGC TTT AGT TGT G-3′ and reverse; 5′-CTC AGT TCT TTC GCA CTG TG-3′ were used.

2.7. Antibodies and reagents

The primary antibodies used in this study are as follows: anti-caspase-11 rat monoclonal antibody (1:200, Abcam), anti-PARP-1 mouse polyclonal antibody (1:500, BD Bioscience), anti-α-tubulin mouse monoclonal antibody (1:4000, Sigma). IFN-γ was purchased from R&D. 3,4-Dihydro-5-[4-(1-piperidinyl)butoxyl]-1(2H)-isoquinoline (DPQ) and 1,5-isoquinolinediol were purchased from Calbiochem. All other reagents were purchased from Sigma unless stated otherwise.

2.8. Statistics

For the statistical analysis, all the experiments were repeated at least three times. The results were expressed as means ± SD of at least three independent experiments, unless stated otherwise. Paired data were evaluated by ANOVA.

3. Results

3.1. Knockdown of PARP-1 suppressed the induction of caspase-11

It has been reported that PARP-1 regulates the induction of proinflammatory genes like iNOS and TNF-α as a transcriptional coactivator of NF-κB [11]. Since induction of caspase-11, a proinflammatory caspase, has been shown to be dependent on NF-κB [7], it is possible that PARP-1 participates in the induction of caspase-11 as well. To test this possibility, we examined the effect of PARP-1 knockdown on the induction level of caspase-11 following LPS stimulation. The MEFs were transfected with control or pLKO.1 vectors containing 21 base-pair hairpin sequences targeting mouse PARP-1. At 48 h after the transfection, the cells were treated with LPS (1 μg/ml) and further incubated for 6 h, followed by immunoblot assay for the detection of caspase-11 and PARP-1. As shown in Fig. 1A, when PARP-1 expression was reduced by RNA interference, the level of caspase-11 protein was reduced by 60% compared to that of control pLKO.1-transfected cells following LPS stimulation. This result suggests that PARP-1 is required for the LPS-induced expression of caspase-11.

To determine whether PARP-1 is required for the transcriptional activation of caspase-11 gene, we examined the mRNA level of caspase-11 in PARP-1 knocked-down MEFs by RT-PCR at 2 h after LPS

(1 μg/ml) stimulation. As shown in Fig. 1B, LPS-induced transcription of caspase-11 mRNA was also reduced by PARP-1 knockdown, suggesting that PARP-1 can regulate the induction of caspase-11 at a transcriptional level.

3.2. PARP-1 was recruited to the caspase-11 promoter following LPS stimulation

To further confirm that PARP-1 regulates the expression of caspase-11 at a transcriptional level, we examined the effect of PARP-1 knockdown on the caspase-11 promoter activity following LPS stimulation. MEFs were transiently transfected with the constructs of PARP-1-pLKO.1 and/or pGL3-caspase-11 promoter encoding the modified firefly luciferase under the putative caspase-11 promoter [7]. Then the cells were stimulated for further 2 h with LPS (1 μg/ml) at 36 h after the co-transfection. As shown in Fig. 2A, knockdown of PARP-1 resulted in the significant reduction of LPS-induced activation of caspase-11 promoter. These results further suggest that PARP-1 regulates the transcription of caspase-11 following LPS stimulation.

Previously, it was reported that PARP-1 functions as a coactivator of NF-κB for the induction of inflammatory genes [11,13]. However, it remains controversial how PARP-1 regulates the activation of NF-κB. To gain insights into how PARP-1 regulates the transcription of caspase-11, we examined whether PARP-1 is recruited to the caspase-11 promoter. We performed ChiP assay using a primer pair detecting 225 base pairs containing three NF-κB-binding sites on the caspase-11 promoter. As shown in Fig. 2B, the chromatins immunoprecipitated with anti-PARP-1 antibody contained caspase-11 promoter region spanning three NF-κB-binding sites. The caspase-11 promoter region was detected only when the cells were stimulated with LPS but not under normal conditions. This result suggests that PARP-1 is recruited to the caspase-11 promoter following NF-κB-activating stimuli.

3.3. Induction of caspase-11 by IFN-γ is independent of PARP-1

Previous studies reported that putative caspase-11 promoter has both NF-κB- and STAT-binding sites and LPS induces the binding of NF-κB whereas IFN-γ induces STAT1 binding on their

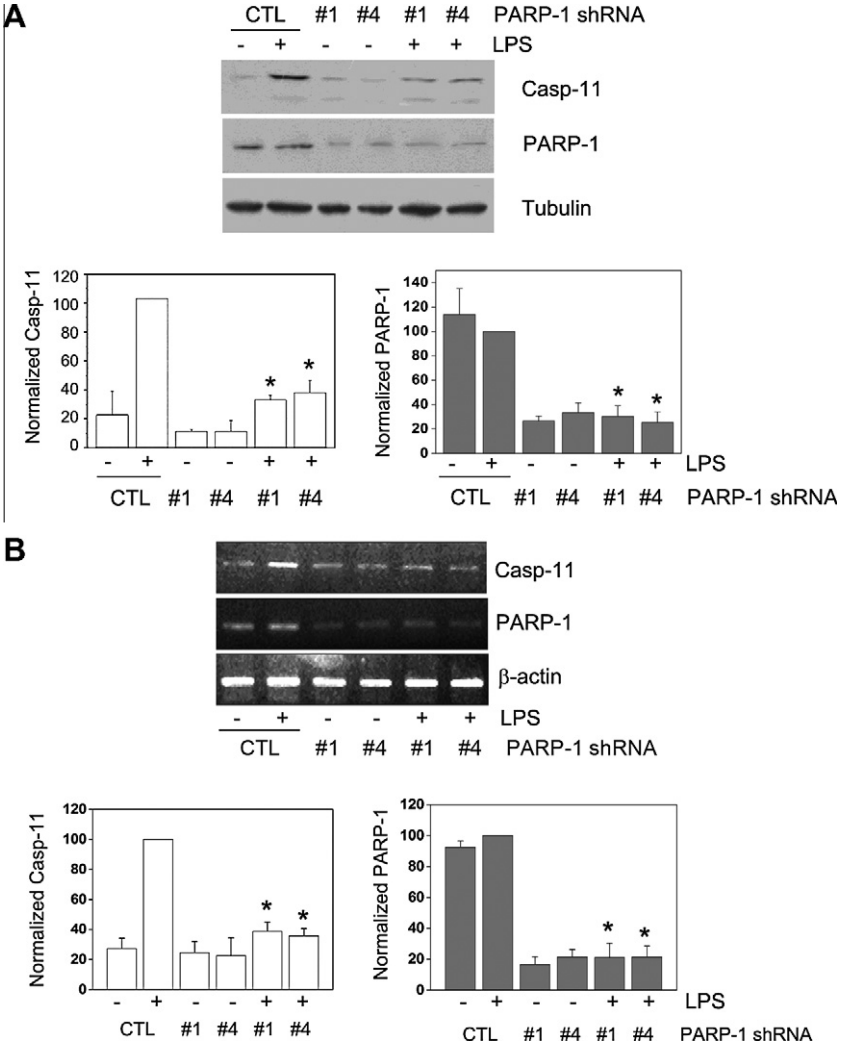

Fig. 1. Knockdown of PARP-1 suppressed the induction of caspase-11 at protein and mRNA levels. (A) To examine if PARP-1 is involved in the regulation of caspase-11 induction, MEFs were transfected with control- (CTL) or PARP-1-pLKO.1 shRNA vectors (#1 and #4). After 48 h, the cells were stimulated with LPS (1 μg/ml) for further 6 h. Then the cells were processed for immunoblot assay using antibodies against caspase-11 (Casp-11), PARP-1 and tubulin. Representative blots are shown in the top panel. The blots from three independent experiments were quantified by densitometric readings of the bands. The reading of maximal level of caspase-11 or PARP-1 served as 100%. The results were presented as means ± SD in the bottom panels. (B) To examine the effect of PARP-1 knockdown on the mRNA level of caspase-11, MEFs were transfected with the control- (CTL) or PARP-1-pLKO.1 shRNA vectors for 48 h and then stimulated with LPS for further 2 h. Then total mRNAs were isolated and processed for semi-quantitative RT-PCR analysis. The band intensities were quantified by densitometric readings. The results were presented in the bottom panels as means ± SD determined from two independent experiments. *Control with LPS vs. PARP-1 shRNA with LPS, $p < 0.001$ by ANOVA.

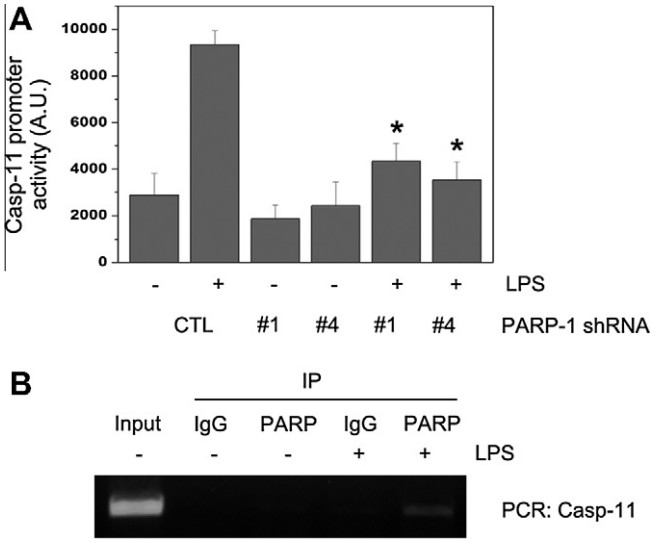

Fig. 2. PARP-1 is recruited to the caspase-11 promoter and regulates its activity. (A) To examine if PARP-1 regulates the promoter activity of caspase-11, MEFs were transfected with control- (CTL) or PARP-1-pLKO.1 shRNA vectors in combination with pGL3-caspase-11 promoter and pRL-TK plasmids for 36 h. Then the cells were stimulated with LPS (1 μg/ml) for further 2 h and dual luciferase activity assay was performed. The results were presented as means ± SD determined from three independent experiments. (A.U., arbitrary unit.) *Control with LPS vs. PARP-1 shRNA with LPS, $p < 0.001$ by ANOVA. (B) To examine if PARP-1 is recruited to the caspase-11 promoter, ChiP assay was performed on the caspase-11 promoter region containing three NF-κB-binding sites using anti-PARP-1 antibody. MEFs were stimulated with LPS (1 μg/ml) for 2 h and then chromatin was isolated, sonicated and then immunoprecipitated (IP) with anti-PARP-1 antibody. Normal rabbit IgG (IgG) was used for immunoprecipitation control. The precipitated material was then subjected to PCR using a primer pair detecting caspase-11 promoter region containing three NF-κB-binding sites. Consistent results were obtained from three independent experiments.

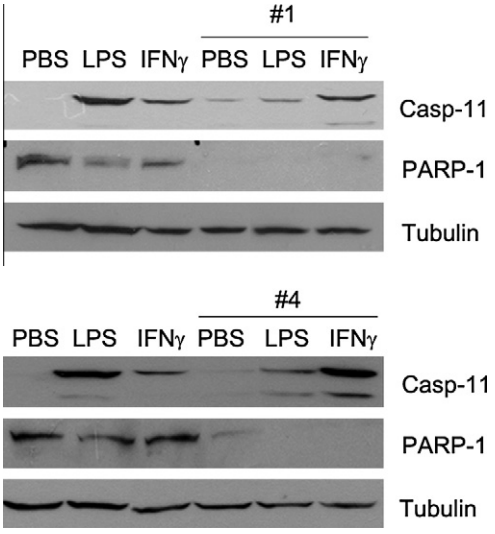

Fig. 3. Induction of caspase-11 by IFN-γ is independent of PARP-1. To examine if PARP-1 is also involved in the IFN-γ-induced caspase-11 expression, MEFs were transfected with control- or two different PARP-1-pLKO.1 shRNA vectors (#1 and #4) for 36 h and then stimulated with LPS (1 μg/ml) or IFN-γ (100 ng/ml) for further 6 h. Then the cells were processed for immunoblot assay using caspase-11 (Casp-11), PARP-1 and tubulin antibodies.

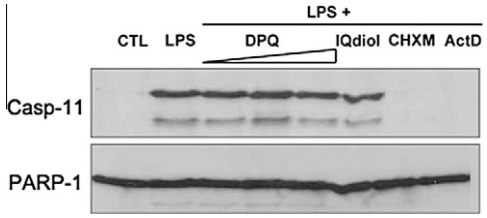

Fig. 4. Pharmacological inhibitors of PARP-1 did not suppress the LPS-induced expression of caspase-11. To examine whether PARP-1 enzymatic activity is required for the induction of caspase-11 following LPS stimulation, MEFs were pretreated with increasing concentration of DPQ (10, 20, and 50 μM) or 1,5-isoquinolinediol (IQdiol, 100 μM) for 1 h and then simulated with LPS (1 μg/ml) for further 6 h. Treatment with cycloheximide (CHXM, 5 μM) or actinomycin D (ActD, 1 μM) served as a control to inhibit caspase-11 induction. Then the cells were processed for immunoblot for caspase-11 and tubulin antibodies. Consistent results were obtained from three independent experiments.

respective binding sites [7,14]. Activation of NF-κB has been shown to be dependent on PARP-1 that functions as a transcriptional coactivator [11,13]. Therefore, it is highly possible that the regulation of caspase-11 expression by PARP-1 as seen in Fig. 1 is mediated by PARP-1 as a coactivator of NF-κB. We reasoned if PARP-1 participates in the activation of caspase-11 promoter as a coactivator of NF-κB, knockdown of PARP-1 would suppress only the NF-κB- but not STAT1-dependent caspase-11 expression. To examine this, MEFs were transfected with PARP-1 shRNA constructs and then stimulated with LPS or IFN-γ, to activate NF-κB or STAT1, respectively. As shown in Fig. 3, PARP-1 knockdown efficiently suppressed the caspase-11 expression induced by LPS. However, IFN-γ-induced caspase-11 expression was not suppressed by PARP-1 knockdown. This result strongly suggests that PARP-1 regulates the expression of caspase-11 as a transcriptional coactivator of NF-κB.

3.4. Regulation of caspase-11 by PARP-1 is independent of PARP-1 enzymatic activity

There have been opposing reports about the requirement of PARP-1 enzymatic activity for the NF-κB coactivator function of PARP-1 [12,13,15–17]. To examine whether PARP-1 enzymatic activity is required for the regulation of LPS-induced caspase-11 expression, levels of caspase-11 expression induced by LPS stimulation in the presence or absence of PARP-1 inhibitors were compared. As shown in Fig 4, both DPQ (10, 20 and 50 μM) and 1,5-isoquinolinediol (100 μM), specific inhibitors of PARP-1, did not suppress the LPS-induced caspase-11 expression. This result indicates that the enzymatic activity of PARP-1 is not required for the caspase-11-inducing function of PARP-1 in MEFs following LPS stimulation.

4. Discussion

In the present study, we present evidence that PARP-1 promotes the induction of caspase-11 gene, possibly functioning as a transcriptional coactivator of NF-κB. Knockdown of PARP-1 resulted in the significant reduction of caspase-11 promoter activity as well as mRNA and protein expression of caspase-11 following LPS stimulation. Importantly, recruitment of PARP-1 to the caspase-11 promoter was observed by ChiP assay. Previous reports presented strong evidence that PARP-1 functions as a transcriptional cofactor for NF-κB to induce proinflammatory genes such as TNF-α and iNOS [11–13]. For this function of PARP-1, it was suggested that DNA-binding or enzymatic activity of PARP-1 is not required [12,13]. However, other reports showed that pharmacological inhibitors of PARP-1 suppressed the PARP-1-activated gene transcription and suggested that automodification of the enzyme is required for its coactivator function for NF-κB [16,17]. Regarding this discrepancy, it has been argued that the inhibitors of PARP-1 can also inhibit other poly(ADP-ribose) polymerases or non-PARP enzymes that can contribute to the activation of proinflammatory response [18]. In addition, since PARP

inhibitors have antioxidant activity [19], it is possible that the inhibitors suppressed the induction of proinflammatory genes in an indirect manner. Our results support the notion that PARP-1 enzymatic activity is not required for the activation of NF-κB since PARP-1 inhibitors did not suppress the LPS-induced caspase-11 expression whereas PARP-1 knockdown efficiently suppressed the caspase-11 induction.

Apart from its well-studied function of chromatin modification, PARP-1 has been shown to regulate the proinflammatory gene transcription via activating transcription factors like NF-κB, activator protein-1, and heat shock factor protein-1 [20]. However, it remains unclear how PARP-1 activates these transcription factors. There has been a recent report that p65 subunit of NF-κB is poly(-ADP-ribosyl)ated and this promoted the nuclear retention of NF-κB dimers [17]. Others reported that direct binding of PARP-1 and NF-κB promoted the assembly of the transcription activation complex [20]. In a recent report, it has been also suggested that PARP-1 binds to the immediate upstream of NF-κB-binding sites and activates the p65 possibly by poly(ADP-ribosyl)ation [21]. We have shown that PARP-1 is recruited to the caspase-11 promoter region containing NF-κB-binding sites, suggesting that PARP-1 binds to the promoter directly or indirectly via forming a complex with NF-κB. In either case, the presence of PARP-1 seems to be required on the caspase-11 promoter for the activation of NF-κB. However, it is not plausible that PARP-1 modifies NF-κB and the modified NF-κB alone is sufficient for the activation of the caspase-11 promoter. Therefore, it remains to be determined whether PARP-1 directly binds to the caspase-11 promoter or indirectly via NF-κB.

A critical role of PARP-1 in the progression of inflammatory diseases has been demonstrated in diverse animal models of inflammation [20]. Caspase-11 has been also implicated in the pathological inflammation and apoptosis [1,4–6]. It has been shown that caspase-11 is required for the activation of caspase-1 that produces mature proinflammatory cytokines like IL-1β and IL-18 [2,3]. Since we observed the induction of caspase-11 is regulated by PARP-1, a part of proinflammatory function of PARP-1 may be mediated by caspase-11.

Recently, it has been shown that caspase-11 has non-pathological function of regulating cell migration [22]. Therefore, it is of importance to understand the induction and activation mechanism of caspase-11 in detail to interfere with its pathological functions only. Therefore, our current observation that PARP-1 was recruited to the caspase-11 only when LPS stimulation was given suggests that promotion of caspase-11 induction by PARP-1 can be a good point of intervention to regulate pathological function of caspase-11.

Acknowledgments

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