Biochemical and Biophysical Research Communications 387 (2009) 115–120

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Suppression of thymus- and activation-regulated chemokine (TARC/CCL17) production by 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose via blockade of NF-κB and STAT1 activation in the HaCaT cells

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ARTICLE INFO

Article history:
Received 11 June 2009
Available online 1 July 2009

Keywords:
PGG
CCL17
TARC
Inflammation
Keratinocyte
NF-κB, STAT1

ABSTRACT

Keratinocytes, one of major cell types in the skin, can be induced by TNF-α and IFN-γ to express thymus- and activation-regulated chemokine (TARC/CCL17), which is considered to be a pivotal mediator in the inflammatory responses during the development of inflammatory skin diseases, such as atopic dermatitis (AD). In this study, we examined the effect of 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (PGG), isolated from the barks of *Juglans mandshurica*, on TNF-α/IFN-γ induced CCL17 expression in the human keratinocyte cell line HaCaT. Pretreatment of HaCaT cells with PGG suppressed TNF-α/IFN-γ-induced protein and mRNA expression of CCL17. PGG significantly inhibited TNF-α/IFN-γ-induced NF-κB activation as well as STAT1 activation. Furthermore, pretreatment with PGG resulted in significant reduction in expression of CXCL9, 10, and 11 in the HaCaT cells treated with IFN-γ. These results suggest that PGG may exert anti-inflammatory responses by suppressing TNF-α and/or IFN-γ-induced activation of NF-κB and STAT1 in the keratinocytes and might be a useful tool in therapy of skin inflammatory diseases.

Introduction

Exposure of the keratinocytes to interferon-γ (IFN-γ) and tumor necrosis factor alpha (TNF-α) leads to abnormal expression of cytokines and chemokines, which is believed to increase infiltration of monocytes/T cells into the site of inflammation in the skin [1,2]. Thymus- and activation-regulated chemokine (TARC/CCL17) is a member of the CC chemokine subfamily that is constitutively expressed in the thymus and is produced by various cell types, including keratinocytes [3]. Since CCL17 is a ligand for CCR4, which is predominantly expressed on Th2 lymphocytes, it selectively controls the migration of Th2 lymphocytes into the site of inflammation. Therefore, CCL17 is considered to be a pivotal mediator in the inflammatory responses during the development of Th2-dominant inflammatory skin diseases such as atopic dermatitis (AD) [3]. Previous studies suggested that serum CCL17 levels reflect the disease progression of AD [4,5]. CCL17 was also shown to be upregulated by keratinocytes in the AD lesional skin [6,7]. Therefore, modulation of CCL17 production in the keratinocytes may contribute to the pathologic processes in inflammatory skin diseases like AD.

1,2,3,4,6-Penta-*O*-galloyl-β-D-glucose (PGG), a bioactive tannin, is present in many medicinal plants and possesses various biological activities such as anti-oxidant, anti-tumor, and anti-viral activities [8–11]. PGG also has anti-inflammatory activity, even though the exact mechanism has not been fully understood. Previous studies of human monocytes stimulated with PMA demonstrated that PGG inhibited the production of IL-8 by inhibition of NF-κB activation and IκB [12]. PGG suppressed TNF-α-induced proinflammatory and adhesion molecules through the inactivation of the NF-κB in human umbilical vein endothelial cells [10]. Furthermore, PGG inhibited inducible nitric oxide synthase and cyclooxygenase-2 activity in LPS-activated macrophages [13]. Therefore, PGG may exert its biological activity by multiple distinct mechanisms depending on the type of stimulus.

In this study, we examine the effect of PGG on TNF-α/IFN-γ-induced CCL17 production in a human keratinocyte cell line HaCaT.

Abbreviations: PGG, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose; TARC, thymus- and activation-regulated chemokine

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doi:10.1016/j.bbrc.2009.06.137

We show that PGG suppressed TNF-α/IFN-γ-induced protein and mRNA expression of CCL-17. We observed for the first time that treatment with PGG not only inhibited TNF-α/IFN-γ-induced activation of NF-κB, but also inhibited activation of STAT1 in the human keratinocytes. In addition, PGG inhibited IFN-γ-induced protein and mRNA expression of Th1 chemokine CXCL9, 10 and 11. These data indicate that PGG can be used as a therapeutic agent for the treatment of skin inflammation.

Materials and methods

Cell culture and reagents. The immortalized human keratinocyte cell line, HaCaT, was maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and antibiotics (100 U/ml penicillin G, 100 μg/ml streptomycin) at 37 °C in a humidified incubator containing 5% CO_2 and 95% air [14]. *N*-α-*p*-Tosyl-L-lysine chloromethyl ketone hydrochloride (TLCK) and BMS-345541 were obtained from Sigma (St. Louis, MO). Jak inhibitor I, AG490, and WHI-P154 were purchased from Calbiochem (La Jolla, CA).

Preparation of PGG. Air-dried barks (3.2 kg) of *Juglans mandshurica* were exhaustively extracted with acetone–H_2O (7:3, v/v) for 72 h at room temperature. Combined aqueous acetone solutions were concentrated under reduced pressure and freeze dried. The crude extracts were suspended in H_2O and fractionated successively with C_6H_{14}, CH_2Cl_2 and EtOAc, respectively. The EtOAc residue (28.4 g) was chromatographed on a Sephadex-LH 20 column washing with MeOH–H_2O (3:1, v/v) to give 3 fractions A1–A3. When treated with MeOH, compound (589 mg) was isolated in A3 fraction as a precipitate. Structure determination of the isolated compound was done by the basis of their spectral data (MALDI-TOF MS, NMR, including COSY, HMQC and HMBC experiments), and by comparison of their spectral data with reported data [15,16].

MTT assay. Cell viability was estimated with a colorimetric assay using MTT [3-(4,5-dimethylthiazol-2-yl]-2-5-dipheyltetrazolium bromide) (Sigma Co. Ltd.).

Immunoblot analysis. Proteins were separated on a 10% SDS–polyacrylamide gel and electrotransferred to a nitrocellulose membrane. The membrane was probed with primary antibodies, followed by horseradish peroxidase-conjugated secondary antibodies and bound antibodies were visualized using ECL reagents. Primary antibodies against p65, IκBα, and actin (Santa Cruz, CA, USA), and total STAT1, phosphor-STAT1, phosphor-p65, and phosphor-IκBα (Cell Signaling Technology, Beverly, MA, USA) were obtained commercially. HRP-conjugated anti-rabbit or goat antibodies were supplied by Sigma (St. Louis, MO).

Transfection. The pGAS-luc construct was purchased from Stratagene (La Jolla CA, USA). The GAS promoter of pGAS-luc construct contains four direct repeats of the IFN gamma-activating sequence (GAS) derived from the guanylate-binding protein (GBP) promoter (nucleotides −123 to −103). Transfection of HaCaT cells with pGAS-luc or pCMV-β-galactosidase construct was carried out using the AMAXA nucleofector according to the manufacturer's instructions (Amaxa biosystems, Germany). After 24 h the cells were harvested, and luciferase and β-galactosidase activities were measured. The luciferase activity of each sample was normalized to the β-galactosidase activity to calculate the relative luciferase activity, and the results were expressed as fold transactivation.

Measurement of chemokines. HaCaT cells were exposed to TNF-α/INF-γ or INF-γ alone in the presence or absence of PGG for 24 h, and chemokines (CCL17, CCL22, CXCL9, 10, and 11) in the supernatants were measured by ELISA kits (R&D Systems, Minneapolis, MN, USA).

RT-PCR analysis. Total RNA was isolated from HaCaT cells using a Trizol reagent kit (Invitrogen, Gaithersburg, MD, USA) according to the manufacturer's instructions [14]. The RNA (2 μg) was reversibly transcribed with 10,000 U of reverse transcriptase and 0.5 μg/μL oligo-$(dT)_{15}$ primer (Promega, Madison, WI, USA). PCR amplification of cDNA aliquots was performed with the following sense and antisense primers (5′–>3′): CCL17 sense, CTT CTC TGC AGC ACA TCC; CCL17 antisense, AAG ACC TCT CAA GGC TTT G; CCL22 sense, AGG ACA GAG CAT GGC TCG CCT ACA GA; CCL22 antisense, TAA TGG CAG GGA GGT AGG GCT CCT GA; CXCL 9 sense, TGC AAG GAA CCC CAG TAG TGA; CXCL 9 antisense, GGT GGA TAG TCC CTT GGT TGG; CXCL 10 sense, GAA CCT CCA GTC TCA GCA CC; CXCL 10 antisense, GCT CCC CTC TGG TTT TAA GGA GAT; CXCL 11 sense, GCT ATA GCC TTG GCT GTG ATA TTG TG; CXCL 11 antisense, CTG CCA CTT TCA CTG CTT TTA CC; β-actin sense, GCG GGA AAT CGT GCG TGA CAT T; and β-actin antisense, GAT GGA GTT GAA GGT AGT TTC GTG. Conditions of PCR amplification were as follows: CCL17, 94 °C, 1 min, 52 °C, 1 min, 72 °C, 1 min for a total of 38 cycles; CCL22, 94 °C, 30 s, 60 °C, 1 min, 72 °C, 30 s for a total of 32 cycles; CXCL9/10/11, 94 °C, 1 min, 55 °C, 1 min, 72 °C, 1 min for a total of 32 cycles. PCR was performed in 50 μL of 10 mmol/L Tris–HCl (pH 8.3), 25 mmol/L $MgCl_2$, 10 mmol/L dNTP, 100 U of Taq DNA polymerase, and 0.1 μmol/L of each primer and was terminated by heating at 70 °C for 15 min. PCR products were resolved on a 1% agarose gel and visualized with UV light after ethidium bromide.

Electrophoretic mobility shift assay (EMSA). HaCaT cells were treated with TNF-α (10 ng/ml) and IFN-γ (10 ng/ml) for 1 h, then nuclear extracts of cells were prepared and analyzed for NF-κB binding activity, as described previously [14].

Statistical analysis. The results were expressed as means ± SEM from at least three independent experiments. The values were evaluated via one-way ANOVA, followed by Duncan's multiple range tests using GraphPad Prism 4.0 software (GraphPad Software, Inc., San Diego, CA, USA). Differences were considered to be significant at $P < 0.05$.

Results

PGG suppressed TNF-α/IFN-γ-induced expression of CCL17 in the HaCaT cells

To exclude the possibility that the cytotoxicity of PGG might contribute to its suppressive effects on CCL17 expression, the cell viability was examined by the MTT assay. As shown in Fig. 1B, PGG had no significant cytotoxic effect on the HaCaT cells at the concentrations tested. Consistent with previous reports [17,18], HaCaT cells were markedly induced to produce CCL17 protein when co-stimulated with TNF-α and IFN-γ. To examine the inhibitory effect of PGG (Fig. 1C), the HaCaT cells were stimulated with TNF-α and/or IFN-γ in the absence or presence of PGG for 18 h, and the production of CCL17 was analyzed by ELISA. TNF-α and/or IFN-γ-induced production of CCL17 by HaCaT cells was significantly inhibited by PGG in a dose-dependent manner. Next, we analyzed the effect of PGG on CCL17 mRNA expression in HaCaT cells stimulated with TNF-α and/or IFN-γ. Consistent with the ELISA results, treatment with PGG suppressed TNF-α and/or IFN-γ-induced mRNA expression of CCL17 in the HaCaT cells. In addition, treatment with PGG suppressed TNF-α and/or IFN-γ-induced protein and mRNA expression of CCL22/MDC, another CCR4 ligand, in the HaCaT cells (data not shown). These results demonstrate that PGG suppressed TNF-α and/or IFN-γ-induced production of CCL17 by human keratinocytes.

Roles of NF-κB and STAT1 activation on CCL17 production induced by TNF-α/INF-γ in HaCaT cells

Since NF-κB and STAT1 are pivotal regulators in TNF-α and IFN-γ-induced immune responses [19,20], we initially monitored acti-

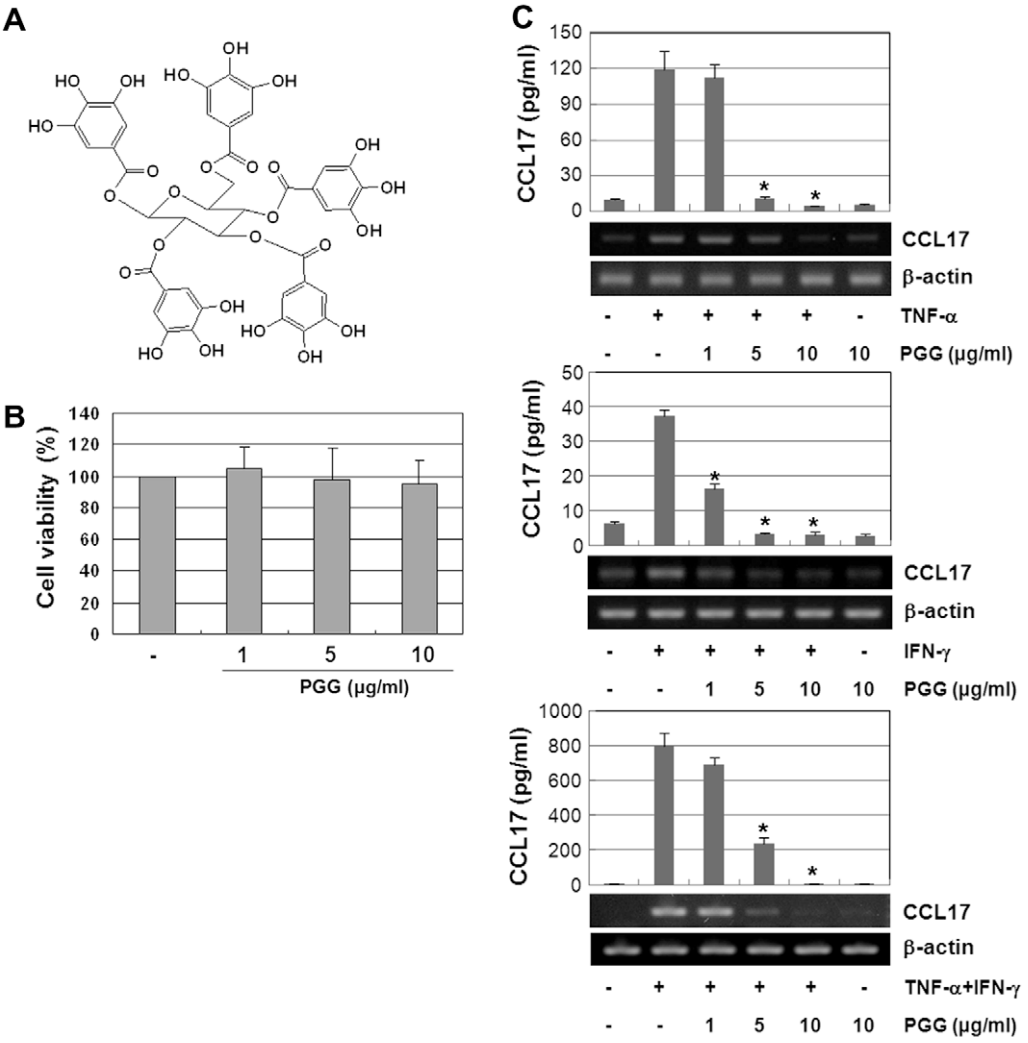

Fig. 1. Effects of PGG on TNF-α and/or IFN-γ-induced expression of CCL17 in HaCaT cells. (A) Chemical structure of 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose. (B) The cells (1×10^5 cells/well) were exposed to PGG at the various concentrations for 24 h. Cell viability was estimated with a colorimetric assay using MTT. (C) HaCaT cells were treated with 1, 5, and 10 μM PGG for 1 h, and then exposed to TNF-α (10 ng/ml) and/or IFN-γ (10 ng/ml) for 18 h. Culture medium of HaCaT cells was harvested. The levels of CCL17 in the culture medium were determined using an ELISA kit. Asterisk indicates statistical significance at $P < 0.001$ as compared with cells treated with TNF-α and/or IFN-γ alone. For analysis of mRNA expression, HaCaT cells treated with PGG for 1 h were exposed to IFN-γ and/or TNF-α for 4 h. Total RNA was extracted. CCL17 and β-actin mRNA were analyzed by RT-PCR using specific primers.

vation of NF-κB and STAT1 in the HaCaT cells treated with TNF-α and/or IFN-γ for various periods of time (Fig. 2). Stimulation with TNF-α increased the phosphorylated form of p65 as well as IκBα degradation in the HaCaT cells. In the IFN-γ-stimulated cells, the phosphorylated form of STAT1 was increased. Co-stimulation with TNF-α and IFN-γ increased the phosphorylated forms of both p65 and STAT1 along with IκBα degradation. Next, we investigated the contribution of NF-κB and STAT1 pathways in TNF-α/IFN-γ-induced CCL17 production. To address this, we used various pharmacological NF-κB inhibitors and JAK/STAT pathway inhibitors. As shown in Fig. 2B, pretreatment with NF-κB inhibitors (TLCK and BMS345541) significantly suppressed TNF-α/IFN-γ-induced CCL17 expression. The inhibitory effects of JAK/STAT pathway inhibitors (Jak inhibitor I, AG490, and WHI-P154) were also observed on TNF-α/IFN-γ-induced CCL17 expression in the HaCaT cells. These results suggest that the signaling cascades that lead to activation of NF-κB and STAT1 are involved in the induction of CCL17 expression in the HaCaT cells costimulated with TNF-α and IFN-γ.

Effect of PGG on NF-κB and STAT1 activation induced by TNF-α/INF-γ in HaCaT cells

We next examined the effect of PGG on these signaling pathways. HaCaT cells were incubated in the absence or presence of PGG for 1 h, and then treated with TNF-α/ IFN-γ. Nuclear extracts or cell lysates from TNF-α/IFN-γ-stimulated cells were analyzed for NF-κB activation. Pretreatment with PGG resulted in a decrease in TNF-α/IFN-γ-induced DNA binding activity of NF-κB (Fig. 3A), nuclear localization of p65, and the phosphorylation levels of p65 (Fig. 3B) in a dose-dependent manner. In addition, PGG significantly inhibited TNF-α/IFN-γ-induced IκBα degradation (Fig. 3B). Next, we examined the effect of PGG on TNF-α/IFN-γ-induced activation of STAT1. As shown in Fig. 3C, PGG almost completely inhibited TNF-α/IFN-γ-induced STAT1 activation. We further evaluated the effect of PGG on GAS promoter activity. HaCaT cells transfected with a pGAS promoter-luciferase construct were stimulated with IFN-γ and luciferase activity was measured (Fig. 3D). Pretreatment of PGG inhibited pGAS promoter activity. These results suggest

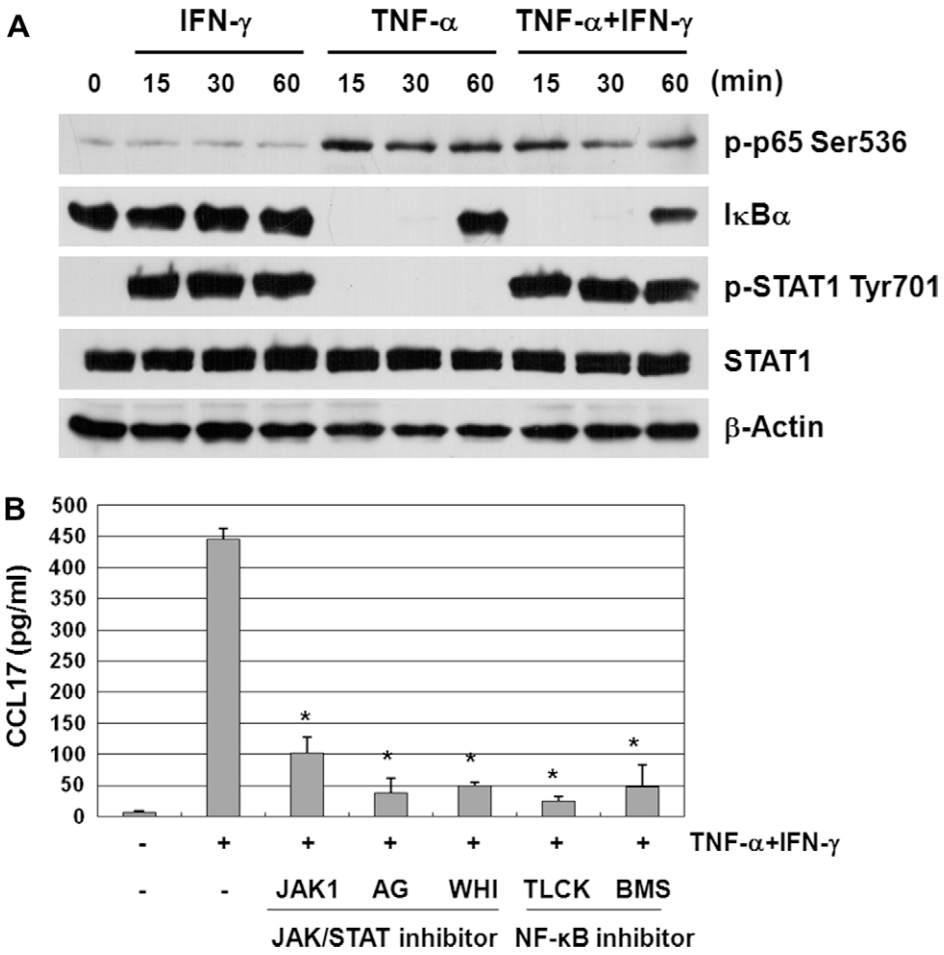

Fig. 2. Roles of NF-κB and STAT1 activation in CCL17 production induced by TNF-α/IFN-γ. (A) HaCaT cells were stimulated with TNF-α (10 ng/ml) and IFN-γ (10 ng/ml) for the indicated times. Cell lysates were prepared from the HaCaT cells treated with TNF-α and IFN-γ and the levels of p65, STAT1 and IκBα were determined by immunoblot analysis. (B) The cells were pretreated with various pharmacological NF-κB inhibitors (TLCK and BMS345541) or JAK/STAT pathway inhibitors (Jak inhibitor I, AG490, and WHI-P154) for 1 h and then stimulated with TNF-α (10 ng/ml) and IFN-γ (10 ng/ml) for 18 h. The levels of CCL17 production in the media were measured by ELISA. Asterisk indicates statistical significance at $P < 0.001$ as compared with cells treated with TNF-α and IFN-γ alone.

that inhibition of TNF-α/IFN-γ-induced CCL17 production by PGG is mediated by the suppression of both NF-κB and STAT1 activation.

Effect of PGG on expression of Th1 chemokines induced by IFN-γ in HaCaT cells

Expression of Th1 chemokines CXCL9, 10, and 11 has been shown to be dependent of activation of transcription factors such as STAT, upon stimulation with IFN-γ [21,22]. We further investigated the effect of PGG on the expression of CXCL9, 10, and 11 in IFN-γ-stimulated HaCaT cells. HaCaT cells were incubated with PGG for 1 h, followed by stimulation with IFN-γ for 24 h, and then the culture supernatants were analyzed for chemokine levels by ELISA. PGG decreased IFN-γ-induced protein expression of CXCL9 and 10 in a dose-dependent manner (Fig. 4A). CXCL11 protein was not significantly produced in our experimental conditions, suggesting that expression and secretion of CXCL11 protein needs other factors in IFN-γ-treated HaCaT cells. Treatment with PGG suppressed IFN-γ-induced mRNA expression of CXCL9, 10, and 11 in the HaCaT cells (Fig. 4B). These results suggest that PGG has inhibitory effects on expression of Th1 chemokines by inhibiting the signaling pathways that lead to activation of STAT1.

Discussion

Since CCL17 plays a critical role in the infiltration $CCR4^+$ lymphocytes in the skin area, the down-regulation of CCL17 production in keratinocytes may be an effective target for treatment of inflammatory skin diseases [3]. Toward this aim, we have examined the biological activity and molecular mechanisms of PGG to modulate CCL17 production in human keratinocyte cell lines. Our results demonstrate that PGG efficiently inhibited production of CCL17 via blockade of NF-κB and STAT1 activation in the TNF-α/IFN-γ-stimulated HaCaT cells .

In the skin, stimulation of the keratinocytes with various stimuli leads to abnormal induction of CCL17 which selectively increases infiltration of $CCR4^+$ lymphocytes into the site of inflammatory tissues [3]. This is one of the characteristic features observed in the development of Th2-mediated inflammatory conditions, like atopic dermatitis. We performed experiments to explore the effect of PGG on the TNF-α/IFN-γ-induced expression of CCL17 in the HaCaT cells. Pretreatment with PGG significantly inhibited mRNA and protein expression of CCL17 in TNF-α/IFN-γ-stimulated HaCaT cells.

Previous studies have reported that various stimuli such as TNF-α and IFN-γ can activate NF-κB activation that is responsible for expression of proinflammatory genes [23]. As shown in Fig. 3,

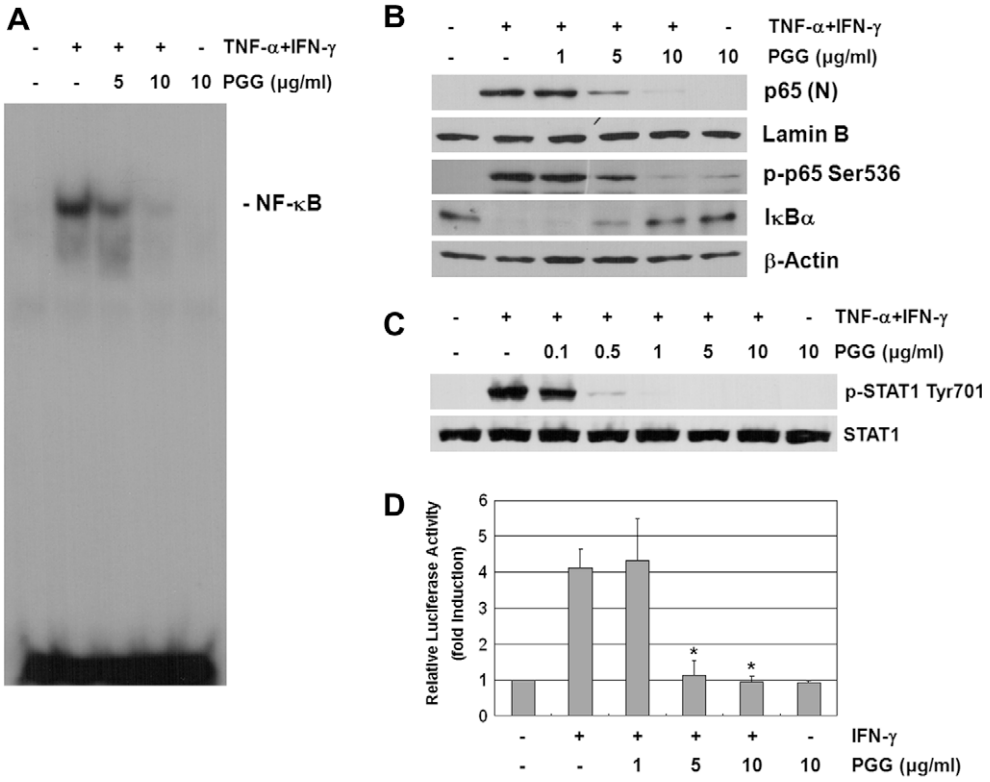

Fig. 3. The effects of PGG on TNF-α/IFN-γ-induced intracellular signaling pathways in HaCaT cells. HaCaT cells were treated with 1, 5 and 10 μM PGG for 1 h, and then stimulated with TNF-α (10 ng/ml) and IFN-γ (10 ng/ml) for 15 min. (A) DNA-binding activity of NF-κB in the nuclear extracts of the cells was measured by EMSA. (B) Cell lysates were prepared from the HaCaT cells treated with TNF-α and IFN-γ and the levels of signaling molecules leading to NF-κB activation were determined by immunoblot analysis. (C) Cell lysates were prepared from the HaCaT cells treated with TNF-α and IFN-γ and the levels of phosphorylated STAT1 were determined by immunoblot analysis. (D) The effect of PGG on the GAS promoter. HaCaT cells were transiently transfected with a GAS promoter-luciferase construct and a β-galactosidase construct (pCMV-lacZ). After 24 h, the transfected cells were treated with PGG for 1 h, stimulated with IFN-γ (10 ng/ml) for 24 h, and the luciferase activity was determined. Luciferase activities are normalized to the β-galactosidase activities and expressed as fold increase over the control. RLA, relative luciferase activity. The results are means ± SD of five separate experiments. Asterisk indicates statistical significance at $P < 0.001$ as compared with cells treated with IFN-γ alone.

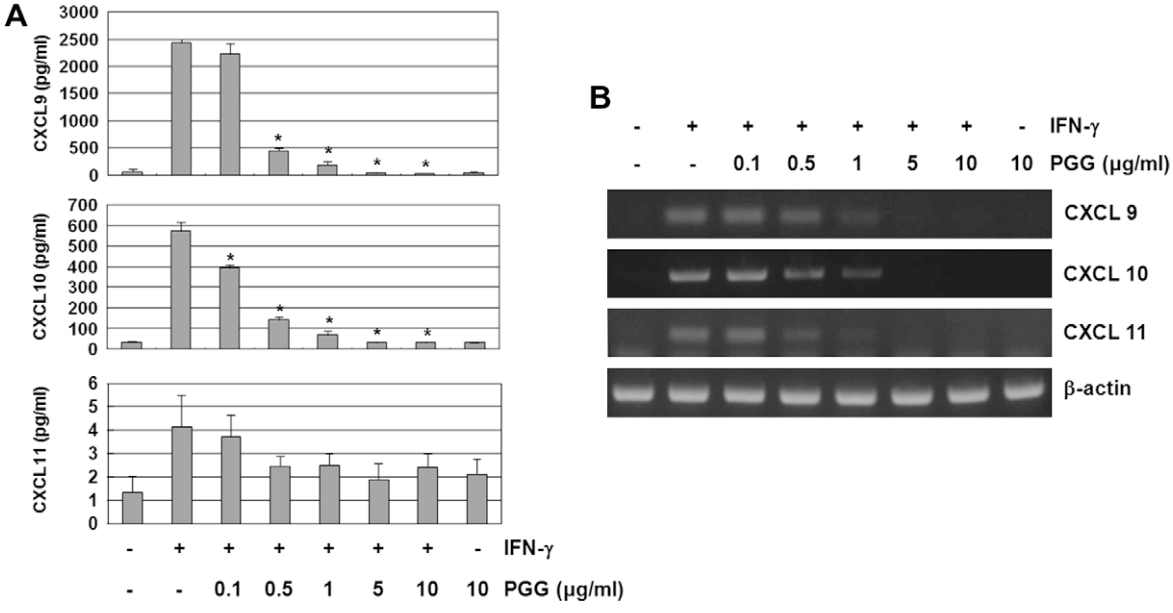

Fig. 4. Inhibition of IFN-γ-induced expression of CXCL9, 10, and 11 by PGG in the HaCaT cells. (A) The cells were incubated with PGG for 1 h and then stimulated with IFN-γ (10 ng/ml) for 24 h. Culture medium of HaCaT cells were harvested and then production of CXCL9, 10, and 11 was measured by ELISA. Asterisk indicates statistical significance at $P < 0.001$ as compared with cells treated with IFN-γ alone. (B) HaCaT cells were treated with PGG for 1 h, and then exposed to IFN-γ for 12 h. Total RNA was extracted. CXCL9, 10, 11, and β-actin mRNA were analyzed by RT-PCR using specific primers.

TNF-α/IFN-γ-induced NF-κB activation and IκBα degradation was significantly inhibited in HaCaT cells treated with PGG, indicating that PGG can affect the NF-κB signaling cascades. Previous studies have documented the inhibition of NF-κB activity by PGG. PGG was shown to inhibit the production of IL-8 through the inactivation of NF-κB in PMA-induced monocytes [12]. Furthermore, PGG inhibited expression of adhesion molecules such as ICAM-1 and VCAM-1 by suppressing NF-κB activation in TNF-α-stimulated endothelial cells [10]. IFN-γ binds to its surface receptor on the target cells and activates Janus kinases (JAK) that then phosphorylate a family of signal transducer and activator of transcription (STAT) proteins [19]. The phosphorylated STAT proteins translocate from the cytoplasm to the nucleus, where they activate expression of target genes, including CCL17. In this study, we showed that the signaling pathways leading to STAT1 activation are necessary for TNF-α/IFN-γ-induced CCL17 production in HaCaT cells (Fig. 2). As shown in Fig. 3, PGG decreased the levels of the phosphorylated STAT1 and GAS promoter activity in TNF-α/IFN-γ-stimulated HaCaT cells. Taken together, our results indicate that PGG has a dual effect on TNF-α/IFN-γ-activated signaling pathways by inhibiting both activation of NF-κB and STAT1.

We performed further experiments to elucidate the inhibitory activity of PGG against expression of IFN-γ-induced chemokines, CXCL9, 10 and 11, which have been shown to be dependent on STAT1 activation [21,22]. Pretreatment with PGG before IFN-γ stimulation significantly inhibited expression of CXCL9, 10 and 11 in the HaCaT cells (Fig. 4). These results indicate that PGG exerts regulatory activities on expression of Th1 chemokines by inhibiting the signaling pathways leading to activation of STAT1.

In summary, we have provided evidence that PGG has inhibitory effects on the CCL17 expression by suppressing the signaling pathways that lead to activation of NF-κB and STAT1 in the TNF-α/IFN-γ-stimulated HaCaT cells. In addition, PGG inhibited IFN-γ-induced expression of CXCL9, 10 and 11. The identification of mechanisms by which PGG regulates expression of chemokines such as CCL17 and its signaling pathways provides a rationale for its application in the treatment of inflammatory skin diseases.

Acknowledgment

This work was supported in part by a Basic Research Program for Forest Science from the Korea Forest Service and by a Hallym University Research Fund (HRF-2009-030).

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