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A novel adipocytokine, chemerin exerts anti-inflammatory roles in human vascular endothelial cells

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ABSTRACT

Chemerin is a recently identified adipocytokine which plays a role on inflammation and adipocytes metabolism. However, its function in vasculature is largely unknown. We examined the effects of chemerin on vascular endothelial inflammatory states. Treatment of human umbilical vein endothelial cells with chemerin (300 ng/ml, 20 min) induced phosphorylation of Akt (Ser473) and endothelial nitric oxide (NO) synthase (eNOS) (Ser1177). Consistently, chemerin increased intracellular cyclic GMP content. Pretreatment with chemerin (1–300 ng/ml, 24 h) significantly inhibited phosphorylation of nuclear factor (NF)-κB p65 (Ser536) and p38 as well as vascular cell adhesion molecule (VCAM)-1 expression induced by tumor necrosis factor (TNF)-α (5 ng/ml, 20 min–6 h). Inhibitor of NF-κB or p38 significantly inhibited the TNF-α-induced VCAM-1 expression. Chemerin also inhibited TNF-α-induced VCAM-1 expression in rat isolated aorta. Moreover, chemerin significantly inhibited monocytes adhesion to TNF-α-stimulated endothelial cells. The inhibitory effect of chemerin on TNF-α-induced VCAM-1 was reversed by a NOS inhibitor. Conversely, an NO donor, sodium nitroprusside significantly inhibited TNF-α-induced VCAM-1. The present results for the first time demonstrate that chemerin plays anti-inflammatory roles by preventing TNF-α-induced VCAM-1 expression and monocytes adhesion in vascular endothelial cells. The effect is mediated via inhibiting activation of NF-κB and p38 through stimulation of Akt/eNOS signaling and NO production.

1. Introduction

Chemerin is a novel adipocytokine with 131–137 amino acids identified in 2007 [1–3]. It is mainly expressed and secreted in adipocytes, but its expression in other tissues including liver, placenta, and ovary is confirmed [2]. Chemerin is originally known as a chemoattractant for immune cells including dendritic cells and macrophages [4]. A G_i protein-coupled receptor, chemokine-like receptor 1 (CMKLR1) is a known receptor for chemerin and this receptor seems to be responsible for the chemotactic effects of chemerin in the immune cells [4–6]. Chemerin is initially secreted as an inactive form, pro-chemerin and processed to an active form via a cleavage of five to nine C-terminal amino acids by serine proteases such as mast cell tryptase and elastase [5]. The functions of chemerin vary dependent on the ways how it is cleaved. For example, chemerin$^{21-157}$ has a strong chemotactic effect and is responsible for an early inflammatory reaction of the immune cells, whereas chemerin$^{21-154}$ is anti-inflammatory via inhibiting macrophage activation [7]. In adipocytes, chemerin stimulates the differentiation and insulin sensitivity [8], whereas it induces the insulin resistance in skeletal muscle, suggesting that the effects of chemerin are different dependent on the tissue types [9]. The blood concentration of chemerin in the obese subjects is reported to be increased [1]. It was further demonstrated that the blood concentration of chemerin is associated with the parameters of obesity and type II diabetes such as body mass index, blood triglyceride level, and blood pressure, implicating its roles in the pathogenesis of diabetes complications and metabolic syndrome [1].

Recently, it was reported that CMKLR1 is expressed in vascular endothelial cells and its expression is up-regulated by tumor necrosis factor (TNF)-α, interleukin (IL)-1β, or IL-6 [10]. However, mechanisms of actions of chemerin on vascular endothelial cells remain to be fully clarified. Therefore, we examined the effects of chemerin on vascular endothelial cells with a special focus on inflammatory responses. In the present study, we observed in human endothelial cells that chemerin can induce nitric oxide (NO) production via activating Akt/endothelial NO synthase (eNOS)

Abbreviations: NO, nitric oxide; eNOS, endothelial NO synthase; NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; CMKLR1, chemokine-like receptor 1; IL-1, interleukin-1; L-NAME, N^G-nitro-L-arginine methyl ester; SNP, sodium nitroprusside; HUVECs, human umbilical vein endothelial cells; cGMP, cyclic GMP.

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pathways. The chemerin-produced NO seems to exert anti-inflammatory effects since it inhibits TNF-α-induced expression of vascular cell adhesion molecule (VCAM)-1 and subsequent monocytes adhesion via suppressing the activation of nuclear factor (NF)-κB and p38 signaling.

2. Materials and methods

2.1. Materials

Reagent sources were as follows: recombinant human chemerin (R&D Systems, Minneapolis, MN, USA), TNF-α (Roche Applied Science, Mannheim, Germany), N^G-nitro-L-arginine methyl ester (L-NAME) (Dojindo, Kumamoto, Japan), SB203580 (Calbiochem, San Diego, CA, USA), pyrrolidine dithiocarbamate, sodium nitroprusside (SNP) (Sigma–Aldrich, St. Louis, MO, USA). Antibody sources were as follows: phospho-p38 (Promega, Madison, WI, USA), phospho-Akt (Ser 473), total Akt, phospho-NF-κB p65 (Ser 536) (Cell Signaling, Beverly, MA, USA), phospho-eNOS (Ser 1177) (BD Biosciences Pharmingen, San Jose, CA, USA), total eNOS, VCAM-1, total p38, total NF-κB p65 (Santa Cruz Biotech, Santa Cruz, CA, USA), total actin (Sigma–Aldrich).

2.2. Cell culture and morphological examination

Human umbilical vein endothelial cells (HUVECs) were purchased from Kurabo (Osaka, Japan) and cultured in Medium 200 supplemented with low serum growth supplement (LSGS; Cascade Biologics, Portland, OR, USA) as described previously [11–13]. Cells at passage 4–16 were used for experiments. HUVECs morphological changes were observed under light microscope (CKX31, Olympus, Tokyo, Japan) equipped with digital camera (SP-350, Olympus).

2.3. Tissue preparation

Male Wistar rats (7–10-week-old) were anesthetized with urethane (1.5 g/kg, i.p.) and euthanized by exsanguination. The thoracic aorta was isolated as described previously [14,15]. After removal of adventitia and fat, aorta was cut into rings for the stimulation and extraction of protein for Western blotting. Animal care and treatment were conducted in conformity with the institutional guidelines of The Kitasato University and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.4. Western blotting

Western blotting was performed as described previously [11–13]. Protein lysates were obtained by homogenizing HUVECs and aortae with Triton-based lysis buffer (1% Triton X-100, 20 mM Tris, pH 7.4, 150 mM NaCl, 1 mM EDTA, 1 mM EGTA, 2.5 mM sodium pyrophosphate, 1 mM β-glycerol phosphate, 1 mM Na_3VO_4, 1 μg/ml leupeptin and 0.1% protease inhibitor mixture; Nacalai Tesque, Kyoto, Japan). Protein concentration was determined using the bicinchoninic acid method (Pierce, Rockford, IL, USA). Equal amounts of proteins (10–15 μg) were separated by SDS–PAGE (7.5%) and transferred to a nitrocellulose membrane (Pall Corporation, Ann Arbor, MI, USA). After blocking with 3% bovine serum albumin or 0.5% skim milk, membranes were incubated with primary antibody (1:500 dilution) at 4 °C overnight, and

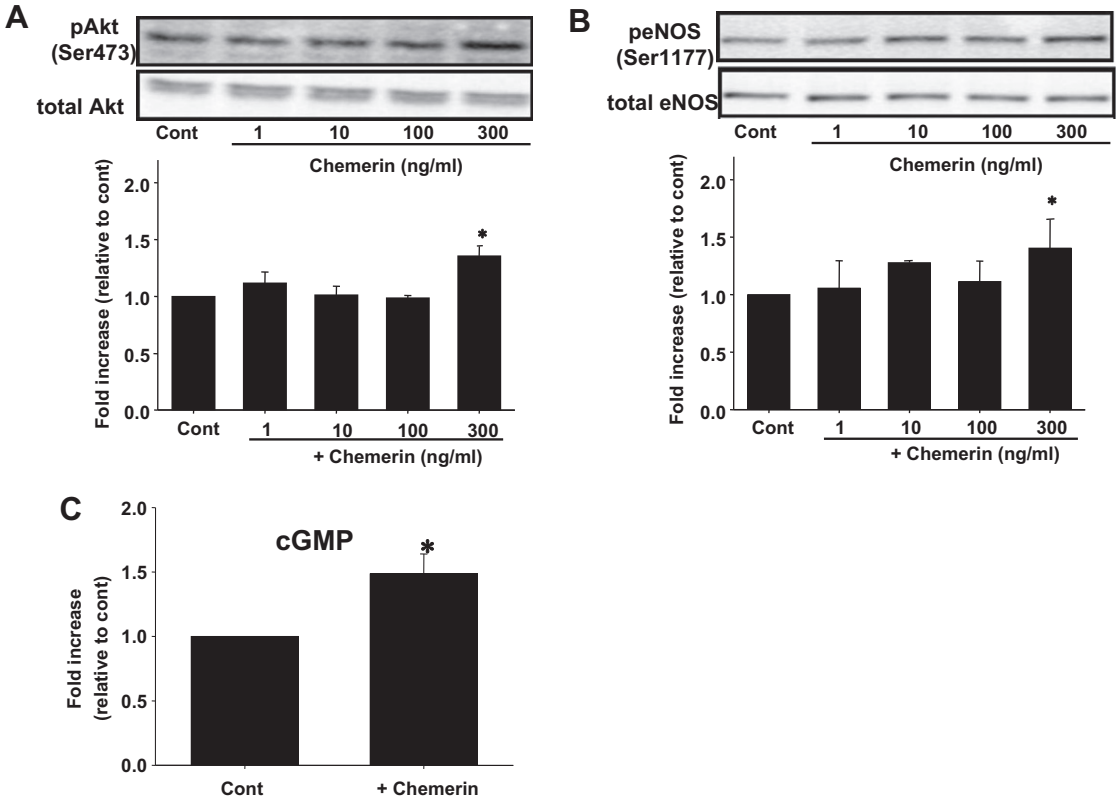

Fig. 1. (A and B) Effects of chemerin on phosphorylation of Akt and endothelial nitric oxide synthase (eNOS) in human unbilical vein endothelial cells (HUVECs). After HUVECs were treated with chemerin alone (1–300 ng/ml, 20 min), phosphorylation of Akt (Ser473) (A: $n = 3$) and eNOS (Ser1177) (B: $n = 4$) was determined by Western blotting. The phosphorylation of Akt and eNOS is shown as fold increase relative to control. (C) Effect of chemerin on intracellular cyclic GMP (cGMP) level in HUVECs. After HUVECs were treated with chemerin alone (300 ng/ml, 10 min), protein lysates were harvested. The cGMP level in the total lysates was measured using cGMP enzyme immune assay kit ($n = 7$). Results are shown as fold increase relative to control. $^*P < 0.05$ vs. cont.

membrane-bound antibodies were visualized using horseradish peroxidase-conjugated secondary antibodies (1:10,000 dilution, 1 h) and the EZ–ECL system (Biological Industries, Kibbutz Beit-Haemek, Israel). Equal loading of protein was confirmed by measuring total protein or actin expression. The results were analyzed using CS Analyzer 3.0 software (ATTO, Tokyo, Japan).

2.5. Cell adhesion assays

HUVECs in a 6-well plate were pretreated with chemerin (300 ng/ml, 24 h) and then stimulated with TNF-α (5 ng/ml, 6 h). After HUVECs were co-incubated with moncytic U937 cells (RIKEN Cell Bank, Tsukuba, Japan) for 1 h, non-adherent cells were removed by several gentle washes with TBS and then the cells were fixed with 4% paraformaldehyde at 37 °C for 10 min. The number of adhering U937 cells was randomly counted in ×200 fields.

2.6. Quantitative measurement of intracellular cyclic GMP (cGMP) level

Intracellular cGMP level in HUVECs was measured using an Enzyme Immunoassay kit (Cayman Chemical Company, Ann Arbor, MI, USA) in accordance to the instructions of the manufacturer. Briefly, after treating HUVECs with chemerin (300 ng/ml) for 10 min, protein lysates were collected and they were acetylated by KOH (4 M) and acetic anhydride. The cGMP content in the lysates was measured at absorbance 410 nm using a standard 96-well plate reader.

2.7. Statistical analysis

Data were shown as mean ± SEM. Statistical evaluations were performed using one-way analysis of variance followed by Tukey's test. Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Effect of chemerin on Akt/eNOS/NO pathways in HUVECs

We first examined whether chemerin activates NO producing pathways which contribute to anti-inflammatory roles of vascular endothelial cells. As shown in Fig. 1A and B, chemerin at 300 ng/ml significantly induced phosphorylation of Akt (Ser473) (1.4 ± 0.1-fold relative to cont, $P < 0.05$, $n = 3$) and eNOS (Ser1177) (1.5 ± 0.1-fold relative to cont, $P < 0.05$, $n = 4$) in HUVECs. Consistent with the results, chemerin (300 ng/ml) significantly augmented the level of intracellular cGMP, which is downstream product of NO/guanylate cyclase (1.5 ± 0.2-fold relative to cont, $P < 0.05$, Fig. 1C, $n = 7$).

3.2. Effect of chemerin on TNF-α-induced expression of VCAM-1 in HUVECs

It was next examined whether chemerin inhibits TNF-α-induced expression of pro-inflammatory adhesion molecule, which mediates monocytes adhesion to vascular endothelium. As shown in Fig. 2A, chemerin pretreatment (300 ng/ml, 24 h) significantly

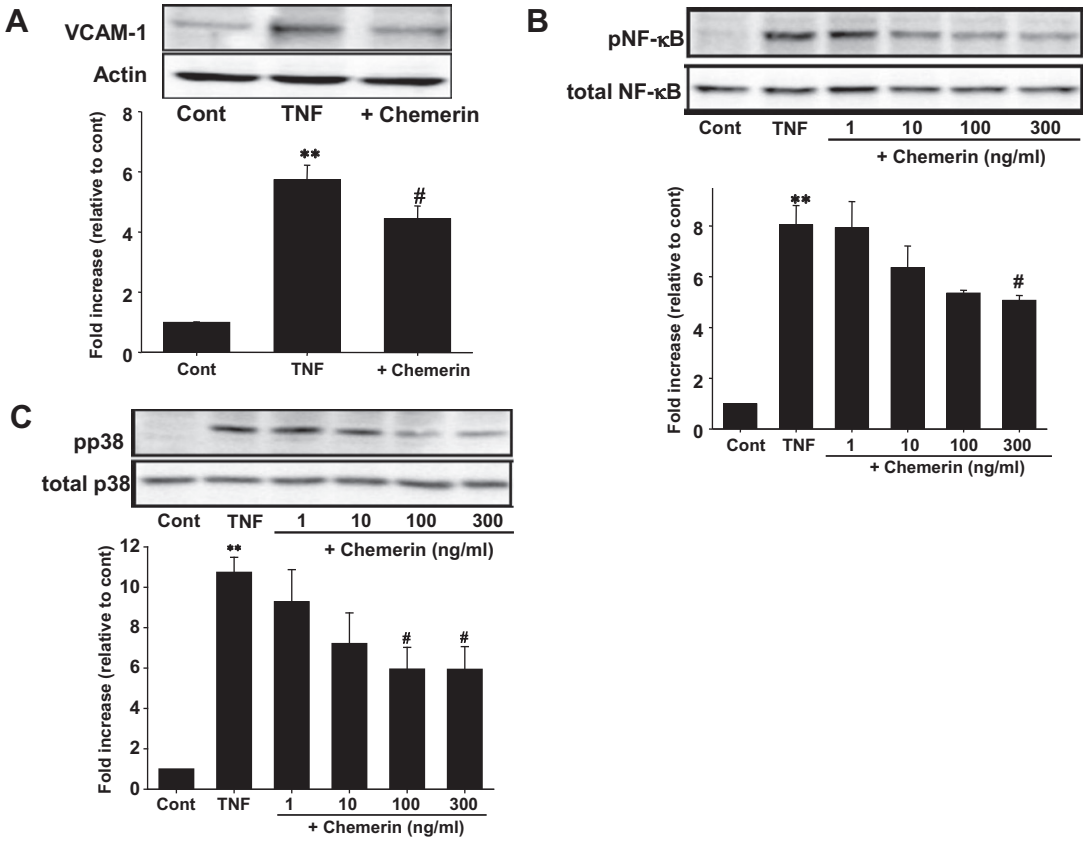

Fig. 2. (A) Effect of chemerin on tumor necrosis factor (TNF)-α-induced expression of vascular cell adhesion molecule (VCAM)-1 in HUVECs. After HUVECs were treated with TNF-α (5 ng/ml) for 6 h in the absence or presence of chemerin (300 ng/ml, pretreatment for 24 h), expression of VCAM-1 was determined by Western blotting ($n = 24$). Equal protein loading was confirmed using total actin antibody. (B and C) Effect of chemerin on TNF-α-induced phosphorylation of nuclea factor (NF)-κB and p38 in HUVECs. After HUVECs were treated with TNF-α (5 ng/ml) for 20 min in the absence or presence of chemerin (1–300 ng/ml, pretreatment for 24 h), phosphorylation of NF-κB p65 (Ser536) (B: $n = 5$) and p38 (C: $n = 6$) was determined by Western blotting. The result is shown as fold increase relative to control. $^{**}P < 0.01$ vs. cont; $^{\#}P < 0.05$ vs. TNF.

inhibited the TNF-α (5 ng/ml, 6 h)-induced expression of VCAM-1 (TNF: 5.7 ± 0.5-fold relative to cont, $n = 24$ vs. TNF + chemerin: 4.4 ± 0.4-fold relative to cont, $n = 24$, $P < 0.05$).

3.3. Effect of chemerin on TNF-α-induced activation of p38 and NF-κB in HUVECs

It was next investigated the upstream signaling pathways for the TNF-α induction of VCAM-1. For this purpose, we measured phosphorylation of p38 and NF-κB p65 (Ser536) using Western blotting. Chemerin pretreatment (1–300 ng/ml, 24 h) concentration-dependently inhibited the TNF-α (5 ng/ml, 20 min)-induced phosphorylation of NF-κB (TNF: 8.2 ± 0.6-fold relative to cont, $n = 5$ vs. TNF + chemerin (300 ng/ml): 4.3 ± 0.9-fold relative to cont, $n = 5$, $P < 0.05$, Fig. 2B) and p38 (TNF: 10.7 ± 0.7-fold relative to cont, $n = 6$ vs. TNF + chemerin (300 ng/ml): 5.9 ± 1.1-fold relative to cont, $n = 6$, $P < 0.05$, Fig. 2C).

3.4. Effect of an NF-κB inhibitor or a p38 inhibitor on TNF-α-induced expression of VCAM-1 in HUVECs

In order to determine if NF-κB and p38 actually mediates TNF-α induction of VCAM-1, we investigated the effect of pretreatment with an NF-κB inhibitor, pyrrolidine dithiocarbamate (10 μM, 30 min) or a p38 inhibitor SB203580 (1 μM, 30 min) on TNF-α (5 ng/ml, 6 h)-induced expression of VCAM-1. Both of the inhibitor significantly attenuated the TNF-α-induced VCAM-1 expression (TNF: 6.4 ± 0.5-fold relative to cont, $n = 9$ vs. TNF + pyrrolidine dithiocarbamate: 5.0 ± 0.5-fold relative to cont, $n = 9$, $P < 0.05$) (TNF: 5.9 ± 0.9-fold relative to cont, $n = 7$ vs. TNF + SB203580: 3.6 ± 0.9-fold relative to cont, $n = 5$, $P < 0.05$).

3.5. Involvement of NO on the inhibitory effect of chemerin on TNF-α-induced VCAM-1 in HUVECs

It was further examined whether chemerin-produced NO could mediate the inhibitory effects on VCAM-1 induction. As shown in Fig. 3A, combined treatment of HUVECs with chemerin (300 ng/ml, 24 h) and a NOS inhibitor, L-NAME (600 μM) reversed the inhibitory effect of chemerin on TNF-α (5 ng/ml, 6 h)-induced VCAM-1 expression (TNF: 5.1 ± 0.5-fold relative to cont, $n = 7$, TNF + chemerin: 3.9 ± 0.4-fold relative to cont, $n = 7$, TNF + chemerin + L-NAME: 5.0 ± 0.6-fold relative to cont, $n = 7$, $P < 0.05$ between TNF and TNF + chemerin, $P < 0.05$ between TNF + chemerin and TNF + chemerin + L-NAME). In addition, pretreatment of HUVECs with an NO donor, SNP (300 μM, 24 h) significantly inhibited the TNF-α-induced VCAM-1 expression (TNF: 6.4 ± 0.5-fold relative to cont, $n = 8$ vs. TNF + SNP: 4.9 ± 0.5-fold relative to cont, $n = 8$, $P < 0.05$, Fig. 3B).

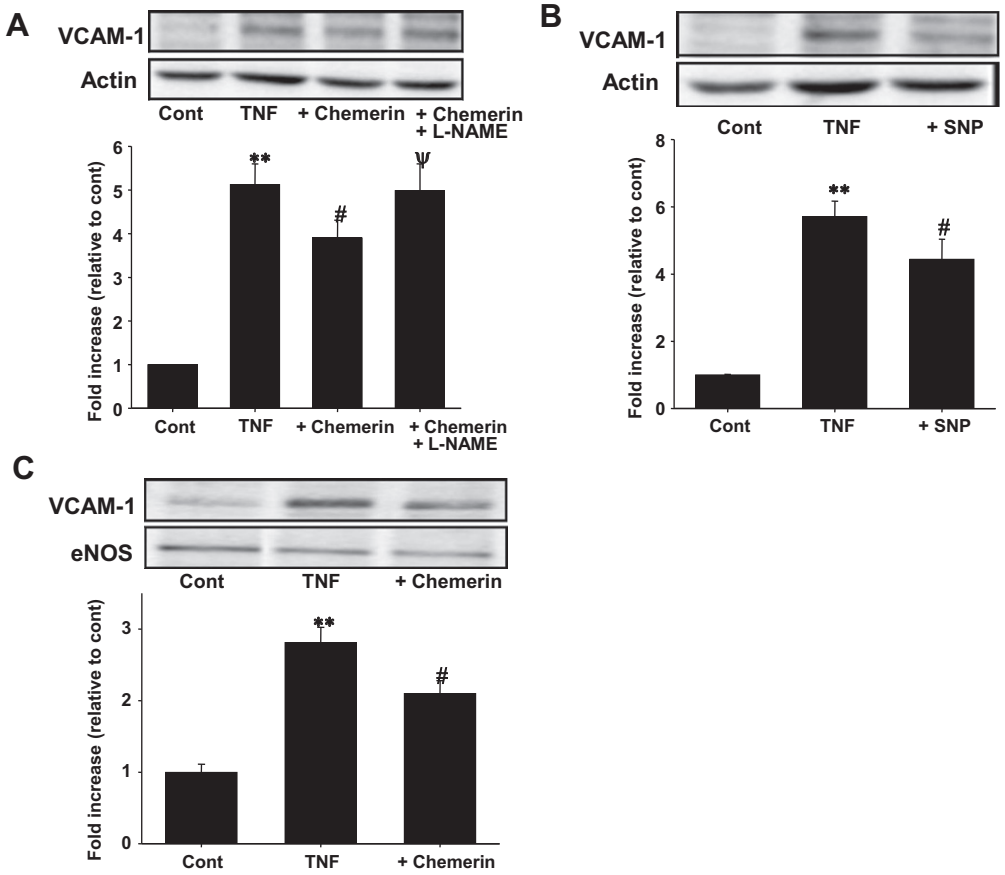

Fig. 3. (A) Effect of a NOS inhibitor on the inhibitory effect of chemerin on TNF-α-induced VCAM-1 expression in HUVECs. After HUVECs were treated with TNF-α (5 ng/ml) for 6 h in the absence or presence of chemerin (300 ng/ml, pretreatment for 24 h) alone or chemerin + N^G-nitro-L-arginine methyl ester (L-NAME; 600 μM), expression of VCAM-1 was determined by Western blotting ($n = 7$). (B) Effect of an NO donor on TNF-α-induced VCAM-1 expression. After HUVECs were treated with TNF-α (5 ng/ml) for 6 h in the absence or presence of sodium nitroprusside (SNP: 300 μM, pretreatment for 24 h), expression of VCAM-1 was determined by Western blotting ($n = 8$). Equal protein loading was confirmed using total actin antibody. (C) Effect of chemerin on TNF-α-induced expression of VCAM-1 in rat isolated aorta. After rat aortae were treated with TNF-α (5 ng/ml) for 6 h in the absence or presence of chemerin (300 ng/ml, pretreatment for 24 h), expression of VCAM-1 was determined by Western blotting ($n = 4$). The expression of VCAM-1 is shown as fold increase relative to control. $^{**}P < 0.01$ vs. cont; $^{\#}P < 0.05$ vs. TNF; $^{\Psi}P < 0.05$ vs. +chemerin.

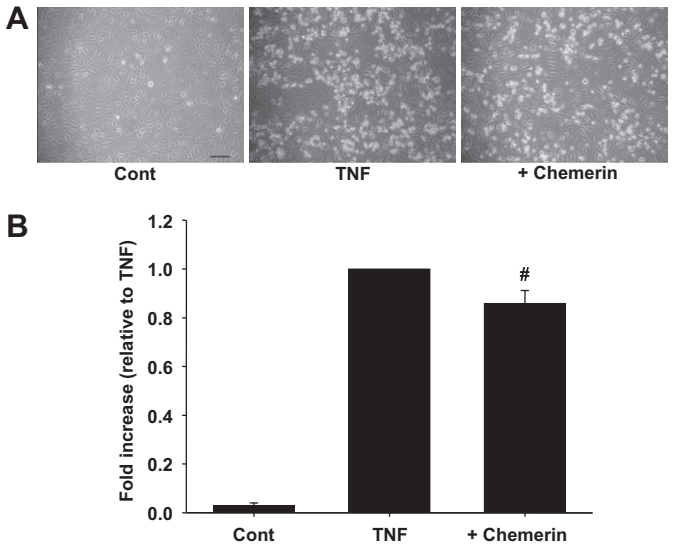

Fig. 4. Effect of chemerin on monocytes (U937 cells) adhesion to HUVECs. (A) Representative photomicrographs of HUVECs pretreated with chemerin (300 ng/ml, 24 h) before TNF-α (5 ng/ml, 6 h) stimulation were shown. After adding U937 cells for 1 h to HUVECs, non-adherent cells were removed by washing and the number of adhering U937 cells was randomly counted (×200 fields). Scale bar: 50 μm. (B) The number of U937 cells adhering to HUVECs is shown as fold increase relative to TNF ($n = 12$). $^{\#}P < 0.05$ vs. TNF.

3.6. Effect of chemerin on TNF-α-induced expression of VCAM-1 in rat isolated aorta

In order to check physiological relevance, it was next examined whether chemerin inhibits TNF-α-induced expression of VCAM-1 in intact vessels. As shown in Fig. 3C, chemerin pretreatment (300 ng/ml, 24 h) significantly inhibited the TNF-α (5 ng/ml, 6 h)-induced expression of VCAM-1 in rat isolated aorta (TNF: 2.8 ± 0.2-fold relative to cont, $n = 4$ vs. TNF + chemerin: 2.1 ± 0.2-fold relative to cont, $n = 4$, $P < 0.05$).

3.7. Effect of chemerin on TNF-α-induced monocytes adhesion to HUVECs

To test whether chemerin could inhibit monocytes adhesion to vascular endothelium, HUVECs were pretreated with chemerin (300 ng/ml, 24 h) before TNF-α stimulation (5 ng/ml, 6 h) and then co-cultured with U937 cells for 1 h. As shown in Fig. 4, chemerin significantly decreased the number of monocytes adhesion to HUVECs (TNF + chemerin: 0.9 ± 0.1-fold relative to TNF, $P < 0.05$, $n = 12$).

4. Discussion

Chemerin is a novel adipocytokine and plays a role not only in the differentiation of adipocytes [3] but also in the inflammatory responses of immune cells such as dendritic cells and macrophages [4]. In the present study, we examined the effects of chemerin on inflammatory states of vascular endothelial cells. The major findings of the present study are that chemerin exerts anti-inflammatory effects in vascular endothelial cells via preventing the TNF-α-induced VCAM-1 expression and subsequent monocytes adhesion through inhibiting the activation of NF-κB and p38. The anti-inflammatory effect is confirmed in the intact blood vessels, and is mediated via the activation of Akt/eNOS/NO pathways. To the best of our knowledge, the results are the first demonstrations and we have clarified the novel vascular effects of chemerin. In humans, the blood chemerin concentration seems to correlate positively with several key factors of metabolic syndrome, such as body mass index, blood triglycerides, and blood pressure [1]. In fact, the blood chemerin concentration increased in severely obese patients [16]. Therefore, it is assumed that chemerin might play a compensate role in the pathogenesis of obesity and/or type II diabetes-related inflammatory vascular diseases.

In the present study, we used the concentrations of chemerin ranging from 1 to 300 ng/ml. It was reported that blood chemerin level is higher in obese subjects (300 ng/ml) compared with that in healthy subjects (220 ng/ml) [1]. Another report has shown that the accumulation of chemerin is higher (370 ng/ml) in the local inflammatory sites of human rheumatoid arthritis [4]. From these reports, it is suggested that the concentrations we used seem to be pathophysiologically relevant. The present study showed that chemerin specifically at 300 ng/ml induced activation of Akt and eNOS. On the other hand, chemerin (1–300 ng/ml) concentration-dependently inhibited the TNF-α-induced activation of NF-κB and p38. This discrepancy may be explained by the idea that anti-inflammatory mechanisms other than Akt/eNOS/NO pathways exist especially at lower concentrations of chemerin.

Previous studies have shown opposite signaling mechanisms of chemerin to the present results. In human microvascular endothelial cells, chemerin was shown to activate p38, ERK and Akt [10]. In human skeletal muscle cells, chemerin was shown to activate p38, NF-κB, and ERK, while chemerin pretreatment inhibits insulin-mediated phosphorylation of Akt [9]. In human visceral adipocytes, chemerin activates ERK [2]. In the present study of HUVECs, chemerin alone treatment activates Akt/eNOS but not ERK (data not shown, $n = 4$), while chemerin pretreatment inhibits the TNF-α-induced NF-κB and p38. These results suggest that effects of chemerin are different dependent on the types of cells. Similarly, the controversial reports exist regarding the effects of chemerin on insulin sensitivity. In human skeletal muscle cells, chemerin causes insulin resistance through the prevention of insulin-mediated glucose uptake [9]. However, in that study, relatively higher concentration of chemerin (1 μg/ml) was used. On the other hand, in mouse 3T3-L1 adipocytes, chemerin rather enhances insulin sensitivity through the activation of insulin signal [8]. Collectively, we presume that chemerin might act as a preventive adipocytokine against the pathogenesis of obesity and/or type II diabetes-related complications not only through the production of vasoprotective NO but also through the enhancement of insulin sensitivity.

In conclusion, the present study has shown that chemerin plays an inhibitory role on inflammatory state of vascular endothelial cells. It was clarified that chemerin inhibits the VCAM-1 expression and monocytes adhesion to vascular endothelial cells by preventing TNF-α-induced phosphorylation of NF-κB and p38. The anti-inflammatory effect of chemerin is mediated via activation of Akt/eNOS/NO pathways. It is suggested that chemerin is a potential drug target against the obesity and/or type II diabetes-related vascular diseases.

Acknowledgments

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