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Original Article

Capmatinib suppresses LPS-induced interaction between HUVECs and THP-1 monocytes through suppression of inflammatory responses

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ABSTRACT

Background: Capmatinib (CAP) is a drug that has been used to treat non-small cell lung cancer (NSCLC) in adults. Presently, its novel effects on skeletal muscle insulin signaling, inflammation, and lipogenesis in adipocytes have been uncovered with a perspective of drug repositioning. However, the impact of CAP on LPS-mediated interaction between human umbilical vein endothelial cells (HUVECs) and THP-1 monocytes has yet to be investigated.

Methods: HUVECs and THP-1 monocytes were treated with LPS and CAP. The protein expression levels were determined using Western blotting. Target protein knockdown was conducted using small interfering (si) RNA transfection. Interactions between HUVECs and THP-1 cells were assayed using green fluorescent dye.

Results: This study found that CAP treatment ameliorated cell adhesion between THP-1 monocytes and HUVECs and the expression of adhesive molecules, such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. Moreover, phosphorylation of inflammatory markers, such as NFκB and IκB as well as TNFα and monocyte chemoattractant protein-1 (MCP-1) released from HUVECs and THP-1 monocytes, was prevented by CAP treatment. Treatment with CAP augmented PPARδ and IL-10 expression. siRNA-associated suppression of PPARδ and IL-10 abolished the effects of CAP on cell interaction between HUVECs and THP-1 cells and inflammatory responses. Further, PPARδ siRNA mitigated CAP-mediated induction of IL-10 expression.

Conclusion: These findings imply that CAP improves inflamed endothelial-monocyte adhesion via a PPARδ/IL-10-dependent pathway. The current study provides *in vitro* evidence for a therapeutic approach for treating atherosclerosis.

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At a glance commentary

Scientific background on the subject

Capmatinib (CAP) is a drug that has been used to treat non-small cell lung cancer (NSCLC) in adults. Presently, its novel effects on skeletal muscle insulin signaling, inflammation, and lipogenesis in adipocytes have been uncovered with a perspective of drug repositioning. However, the impact of CAP on LPS-mediated interactions between human umbilical vein endothelial cells (HUVECs) and THP-1 monocytes has yet to be investigated.

What this study adds to the field

CAP improves inflamed endothelial-monocyte adhesive interactions via a PPARδ/IL-10-dependent pathway. The current study provides *in vitro* evidence for a therapeutic approach for treating atherosclerosis.

Introduction

Cardiovascular diseases mainly result from atherosclerosis-mediated complications caused by a chronic inflammatory state, associated with abnormal proliferation of endothelial and vascular smooth muscle cells [1]. Atherosclerosis is characterized by vascular inflammation, endothelial dysfunction, and accumulation of lipid, cholesterol, and calcium in the intima of large- and medium-sized muscular arteries, forming plaques [1]. The interplay between vascular smooth muscle cells and macrophages has a role in the development of atherosclerosis [2].

Cardiovascular disease and cancer are the two leading chronic diseases causing death worldwide [3,4]. These diseases share various molecular signaling pathways associated with pathogenic developmental processes, such as genetic alteration, environmental factors, and lifestyle [5]. Notably, cancer development is caused by several molecular mechanisms catalyzed by the same elements for atherosclerosis [5]. Although these two diseases may seem unrelated at first glance, a thorough analysis of its molecular mechanisms have clarified significant similarities and show evidence of a close relationship [5,6].

Capmatinib (CAP), a c-Met inhibitor, is a medication for treating metastatic non-small cell lung cancer in adults with the MET gene mutation [7]. CAP has been reported to attenuate diethylnitrosamine [8] or acetaminophen [9]-induced inflammation in mice through downregulation of serum pro-inflammatory cytokines, such as TNFα and IL-1β. CAP suppresses inflammation via a PPARδ/p38-dependent pathway, thereby attenuating insulin resistance in skeletal muscle cells [10]. Furthermore, Ahn et al. found that CAP inhibits lipogenesis in 3T3-L1 adipocytes through an AMP-activated protein kinase (AMPK)-dependent mechanism [11]. These studies denote that CAP has anti-inflammatory and anti-metabolic syndrome properties.

Based on the association between cancer and atherosclerosis and the anti-inflammatory effect of CAP, we performed the current study to demonstrate that CAP attenuates inflammatory responses in endothelial cells, thereby suppressing its adhesion with monocytes using human umbilical vein endothelial cells (HUVECs) and THP-1 monocytes. Furthermore, CAP-associated molecular mechanisms are also revealed.

Material and methods

Cell culture and treatments

HUVECs (ATCC, Manassas, VA, USA) were grown in M200PRF medium (Invitrogen, Carlsbad, CA, USA) supplemented with a low-serum growth supplement mixture on 0.3% gelatin-coated culture plates (Invitrogen). THP-1, human monocytes (ATCC, Manassas, VA, USA) were cultivated in RPMI 1640 media containing 10% fetal bovine serum, 100 U/mL penicillin, and 100 g/mL streptomycin (Invitrogen). At 37 °C, cells were grown in a humidified environment containing 5% CO_2. For all investigations, cells at passages 4–5 were employed. Lipopolysaccharide (LPS) (Sigma, St. Louis, MO, USA) was dissolved in phosphate-buffered saline (PBS; Biosesang, Seoul, Republic of Korea). HUVECs and THP-1 cells were treated with 0–10 nM CAP (Selleckchem, Houston, TX, USA) for 24 h. For co-culture, THP-1 monocytes were harvested and culture medium was removed by suction. Treatment of HUVECs with suspension of THP-1 cells with M200PRF (1×10^4) for 30 min was performed for cell adhesion assay.

Immunoblotting

Cultured cells were extracted and lysed for 60 min at 4 °C in cell lysis buffer (Intron Biotechnology, Seoul, Republic of Korea). Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed on equal amounts of proteins (30–40 μg) using 10% gel. The extracted proteins were separated and put to a nitrocellulose membrane (Amersham Bioscience, Westborough, MA, USA). The transferred membranes were probed with the corresponding primary antibodies, followed by binding with secondary antibodies linked to horseradish peroxidase (Santa Cruz Biotechnology). An enhanced chemiluminescence kit was used to detect immunoreactive signals (Amersham Bioscience).

Antibodies

The antibodies used were as follows: anti-ICAM-1 (1:1000), anti-VCAM-1 (1:1000), anti-E-selectin (1:1000), anti-phospho NFκB (1:1000), anti-NFκB (1:2500), anti-phospho IκB (1:1500), anti-PPARδ (1:1500), anti-IL-10 (1:1500), and anti-β-actin (1:2000) were purchased from Santa Cruz Biotechnology.

Gene knock-down in cells

The small-interfering RNA (siRNA) oligonucleotides (20 nM) selective for PPARδ (PPARδ siRNA) and IL-10 (IL-10 siRNA) were procured from Santa Cruz Biotechnology. Cultured cells were transfected with PPARδ siRNA or IL-10 siRNA using Lipofectamine 3000 (Invitrogen), according to the manufacturer's directions. In brief, the cells were grown until they were 85% confluent. The cells were serum-starved for 12 h before being transfected with 20 nM siRNAs. Protein extraction was performed on the transfected cells.

Enzyme linked immunosorbent assay (ELISA)

The culture supernatant of cells was stored at −70 °C for further ELISA. The TNFα and MCP-1 as well as IL-10 levels in the cell culture media were quantified using ELISA kits (R&D Systems, Minneapolis, MN, USA) for each protein following the manufacturer's instructions.

Cell adhesion assay between HUVECs and THP-1 monocytes

LPS (200 ng/mL) and CAP (0–5 nM) were given to HUVECs for 24 h. Then, the treated HUVECs were co-cultured with THP-1 monocytes that had been tagged with the green fluorescent dye by incubating with 10 μg/mL 2,7-bis (2-carboxyethyl)-5(6)-carboxyfluorescein acetoxymethylester (Invitrogen) for 30 min at 37 °C. THP-1 cells were washed twice with phosphate-buffered saline (PBS) after co-culture with HUVECs for 30 min. THP-1 cells on HUVECs were observed using fluorescence microscopy. Adhered THP-1 monocytes (green dots) were calculated as follows: adhered THP-1 cells (%): [(number of THP-1 cells co-cultured with HUVECs) - (number of washed out THP-1 cells)]/(number of THP-1 cells co-cultured with HUVECs) × 100. Number of THP-1 cells co-cultured with HUVECs was 1×10^4.

Statistical analyses

The data is provided as a set of relative values. Analyses were conducted using one-way ANOVA, which was followed by post hoc analysis. All statistical analyses were conducted using GraphPad Prism version 7 for Windows (La Jolla, CA, USA). Results are presented as the fold of the highest values (means ± SD) or the absolute values. At least three replicates of each experiment were performed. Protein expression levels in Western blotting images were quantified using Image J software (NIH, Rockville, MD, USA). All proteins were normalized by β-actin. Phospho-NFκB was normalized by total NFκB. Statistical significance was assessed using one-way repeated ANOVA and Tukey's post hoc tests.

Results

CAP inhibits the adhesion between monocytes and endothelial cells and the expression of adhesive molecules in endothelial cells

First, we performed a cell viability assay in HUVECs and THP-1 cells to determine treatment concentration of CAP. Cell viabilities were not affected by 0–5 nM CAP. However, a significant decrease in viable cells was noticed at 10 nM CAP in both cell types [Fig. 1A]. Adhesion and migration of monocytes are known to be enhanced at the beginning of atherosclerotic plaque formation [12,13]. Thus, we used cell culture to investigate the impact of CAP on the adhesion between endothelial

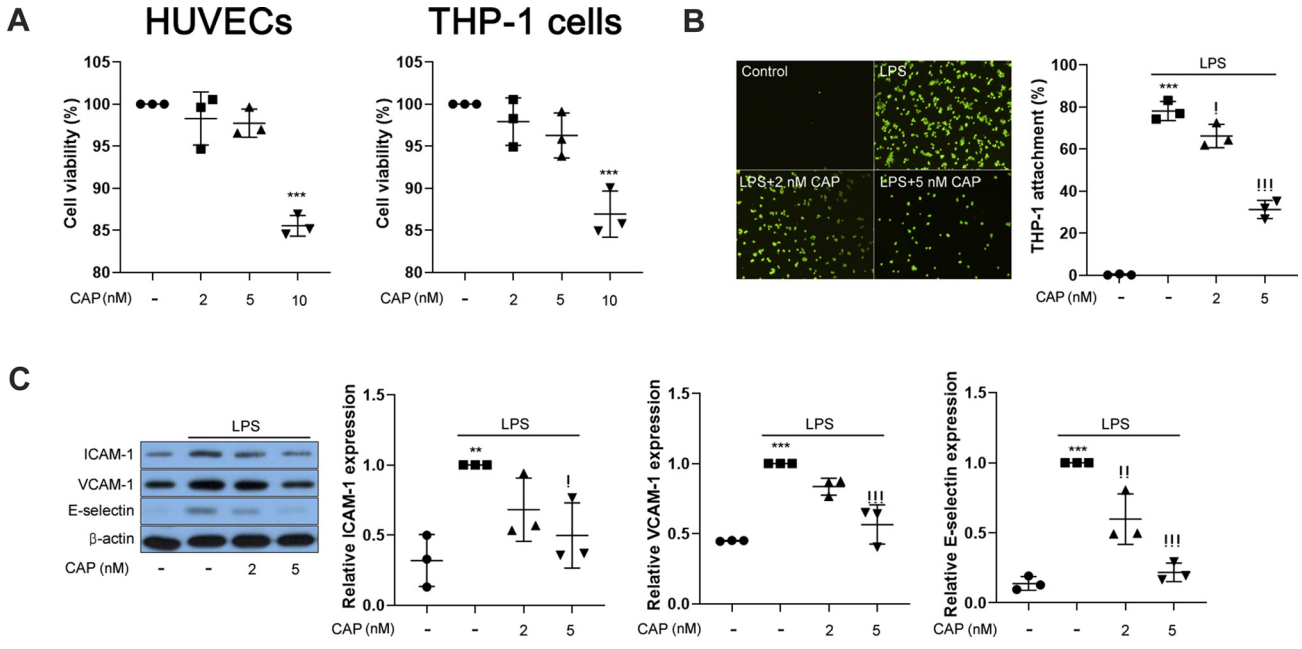

Fig. 1 **CAP reduces monocyte adhesion on endothelial cells as well as adhesion molecule expression in endothelial cells.** (A) MTT assay in HUVECs and THP-1 cells treated with 0–10 nM CAP for 24 h. THP-1 cell adhesion assay (B) and Western blotting of ICAM-1, VCAM-1, and E-selectin (C) in HUVECs treated with LPS (200 ng/mL) and 0–5 nM CAP for 24 h ***$p < 0.001$ when compared to control. $^{!!!}p < 0.001$, $^{!!}p < 0.01$, and $^{!}p < 0.05$ when compared to LPS.

cells and monocytes. We confirmed that LPS upregulated the adhesion of THP-1 monocytes to HUVECs. However, CAP treatment reversed dose-dependently this change [Fig. 1B]. In HUVECs, CAP treatment dose-dependently inhibited LPS-induced expressions of adhesive molecules, such as ICAM-1, VCAM-1, and E-selectin [Fig. 1C].

CAP ameliorates inflammatory responses in LPS-treated endothelial cells and monocytes

Inflammation is a crucial factor in the progression of atherosclerosis [14]. We found that 200 ng/mL LPS for 24 h did not affect cell viability in HUVECs and THP-1 cells [Suppl. Fig. 1]. Treatment with CAP attenuated LPS-induced inflammatory markers, such as phosphorylated NFκB and IκB expression in HUVECs and THP-1 cells [Fig. 2A]. Furthermore, LPS mediated the release of pro-inflammatory cytokines, such as TNFα and MCP-1, to culture media of HUVECs and THP-1 monocytes [Fig. 2B].

PPARδ is involved in CAP's impact on inflammation in HUVECs and THP-1 cells

PPARδ exerts suppressive effects on atherogenic inflammation [15–17]. We found that treatment with CAP enhanced the expression of PPARδ in HUVECs and THP-1 monocytes [Fig. 3A]. siRNA-associated suppression of PPARδ reduced the effects of CAP on LPS-mediated attachment of THP-1 monocytes on HUVECs and adhesion molecules in HUVECs (Fig. 3B,C). Moreover, the inhibitory effects of CAP on LPS-induced NFκB and IκB phosphorylation were mitigated by PPARδ siRNA [Fig. 3D]. Corresponding to these results, PPARδ siRNA weakened the impact of CAP on the release of TNFα and MCP-1 to culture media of LPS-treated HUVECs and THP-1 monocytes [Fig. 3E].

PPARδ/IL-10 signaling participates in the effects of CAP on monocytes and endothelial cells

IL-10 is a cytokine with anti-inflammatory properties, which appears to play a preventive role in developing atherosclerosis [18,19]. Treatment with CAP increases IL-10 expression in HUVECs and THP-1 cells as well as release of IL-10 [Fig. 4A]. IL-10 siRNA abrogated CAP-mediated suppression of adhesion of THP-1 monocytes to HUVECs [Fig. 4B,C] and inflammatory responses [Fig. 4D,E] in these two cell types. In addition, siRNA for IL-10 did not affect PPARδ expression, whereas PPARδ siRNA mitigated CAP-induced IL-10 expression in HUVECs [Fig. 4F].

Discussion

Atherosclerosis is the leading cause of vascular death around the world. Furthermore, it is a severe health problem with poor prognosis and reduction of life expectancy [20]. In the current study, we have demonstrated several novel findings as follows. 1) CAP treatment inhibited the adhesion between HUVECs and THP-1 monocytes and expression of adhesion molecules in HUVECs; 2) Treatment with CAP suppressed inflammatory responses in HUVECs and THP-1 monocytes in the presence of LPS; 3) Treatment of CAP dose-dependently augmented PPARδ and IL-10 expression in both cell types; 4) siRNA for PPARδ or IL-10 attenuated the effects of CAP on the adhesion between HUVECs and THP-1 monocytes and inflammation in HUVECs and THP-1 cells under the LPS conditions.

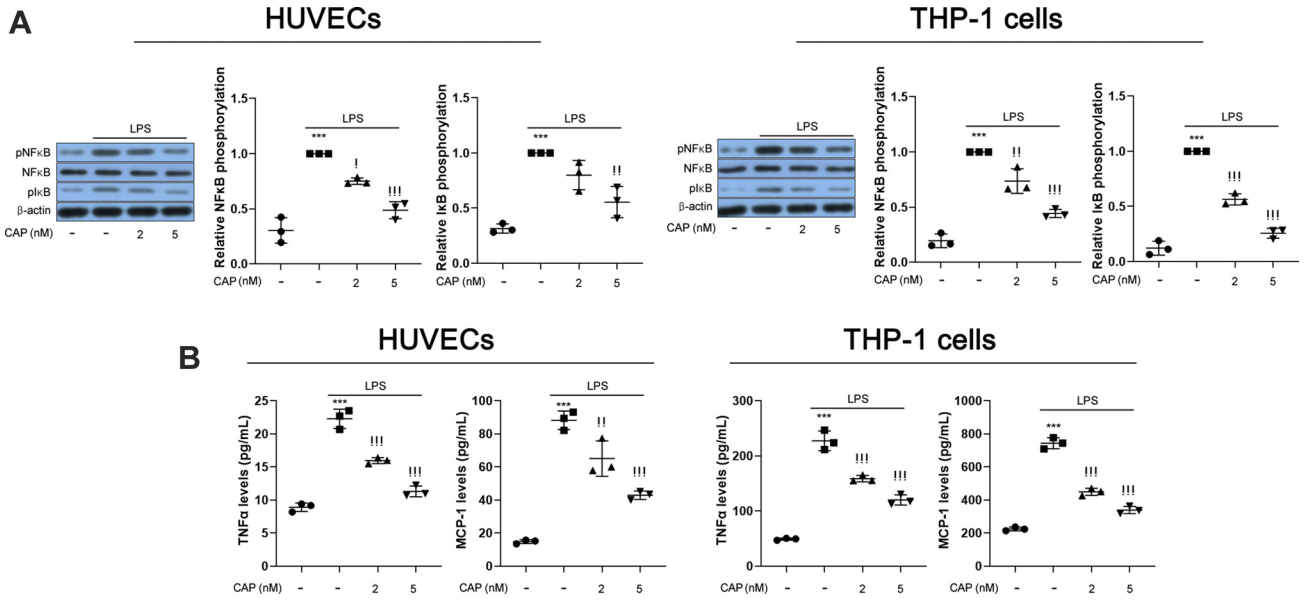

Fig. 2 **CAP ameliorates inflammatory responses in LPS-treated HUVECs and THP-1 monocytes.** (A) Western blot analysis of phosphorylated NFκB and IκB in HUVECs and THP-1 cells treated with LPS (200 ng/mL) and 0–5 nM CAP for 24 h. (B) ELISA of TNF and MCP-1 in culture media of HUVECs and THP-1 cells treated with LPS (200 ng/mL) and 0–5 nM CAP for 24 h ***$p < 0.001$ when compared to control. $^{!!!}p < 0.001$, $^{!!}p < 0.01$, and $^{!}p < 0.05$ when compared to LPS.

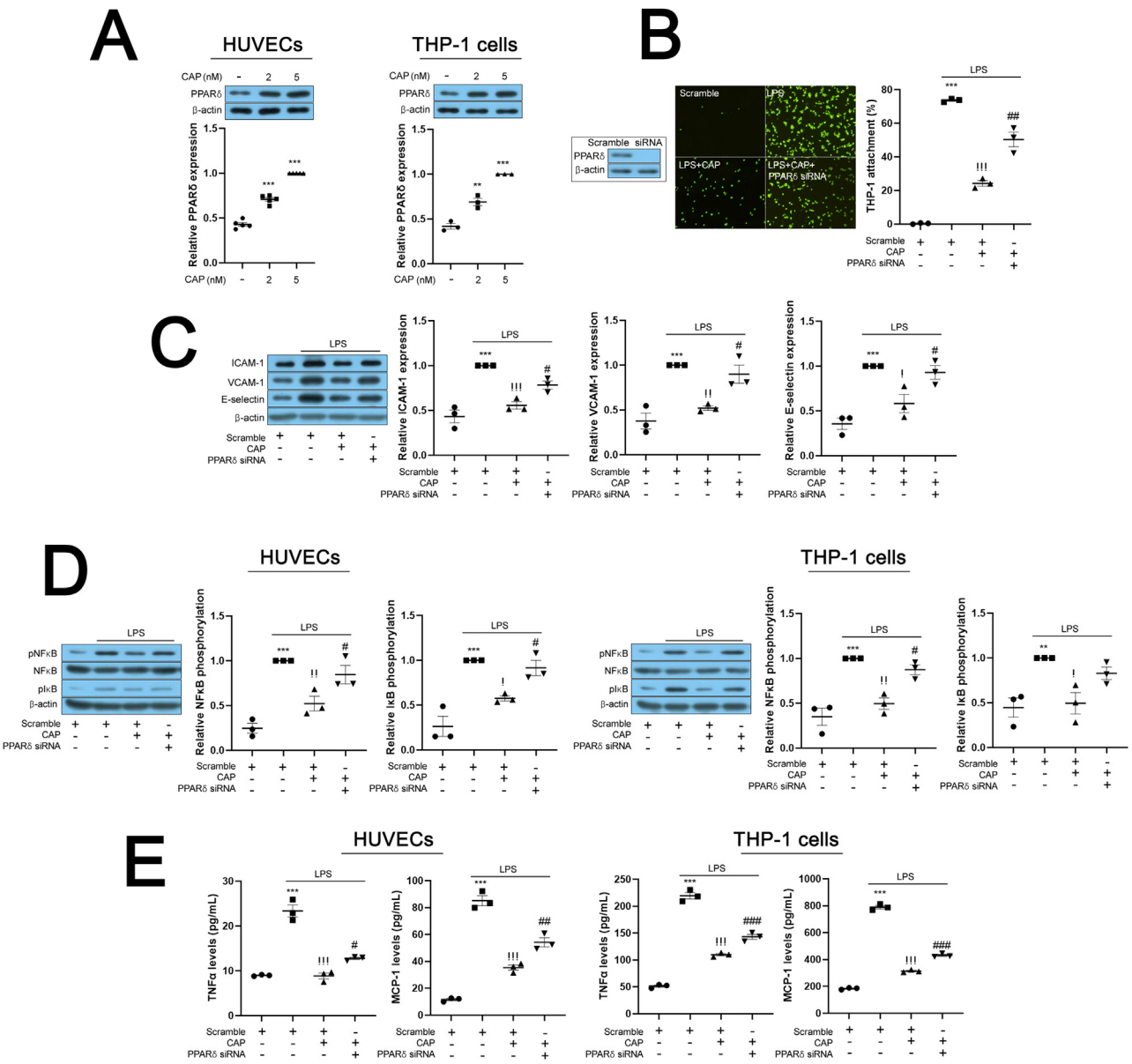

Fig. 3 **CAP attenuates the adhesion between HUVECs and THP-1 monocytes as well as inflammation through PPARδ-dependent signaling.** (A) Western blot analysis of PPARδ in HUVECs and THP-1 cells treated with 0–5 nM CAP for 24 h. THP-1 cell adhesion assay (B) and Western blotting of ICAM-1, VCAM-1, and E-selectin (C) in scrambled or PPARδ siRNA (20 nM)-transfected HUVECs treated with LPS (200 ng/mL) and CAP (5 nM) for 24 h. (D) Western blot analysis of phosphorylated NFκB and IκB in scrambled or PPARδ siRNA (20 nM)-transfected HUVECs and THP-1 cells treated with LPS (200 ng/mL) and CAP (5 nM) for 24 h. (E) ELISA of TNF and MCP-1 in culture media of scrambled or PPARδ siRNA (20 nM)-transfected HUVECs and THP-1 cells treated with LPS (200 ng/mL) and CAP (5 nM) for 24 h $^{***}p < 0.001$ and $^{**}p < 0.01$ when compared to control. $^{!!!}p < 0.001$, $^{!!}p < 0.01$, and $^{!}p < 0.05$ when compared to LPS. $^{\#\#\#}p < 0.001$, $^{\#\#}p < 0.01$, and $^{\#}p < 0.05$ when compared to LPS plus CAP.

Inflammation is a major contributor to the development of atherosclerosis by generating arterial plaques [14,21]. Macrophage infiltration (primarily derived from circulating monocytes) disrupts atherosclerotic plaques in fatal acute myocardial infarction. Macrophage infiltration-mediated atherosclerotic plaque destabilization [21] causes upregulation of pro-inflammatory cytokines and lytic proteins, thereby rupturing the plaque's fibrous cap [22]. As a result, proper inflammation management could be a therapeutic strategy for treating atherosclerosis and its complications. In the presence of LPS, we discovered that CAP treatment reduced THP-1 monocyte adherence to HUVECs and inhibited the expression of adhesion molecules in HUVECs. Treatment of HUVECs and THP-1 cells with CAP attenuated LPS-induced inflammatory responses, such as NFκB and IκB phosphorylation, as well as TNFα and MCP-1 secretion. These results may reveal that CAP attenuates the inflammatory response and adhesion between endothelial cells and monocytes, a typical pathological phenomenon associated with atherosclerosis, showing the potential of CAP as a therapeutic agent for atherosclerosis.

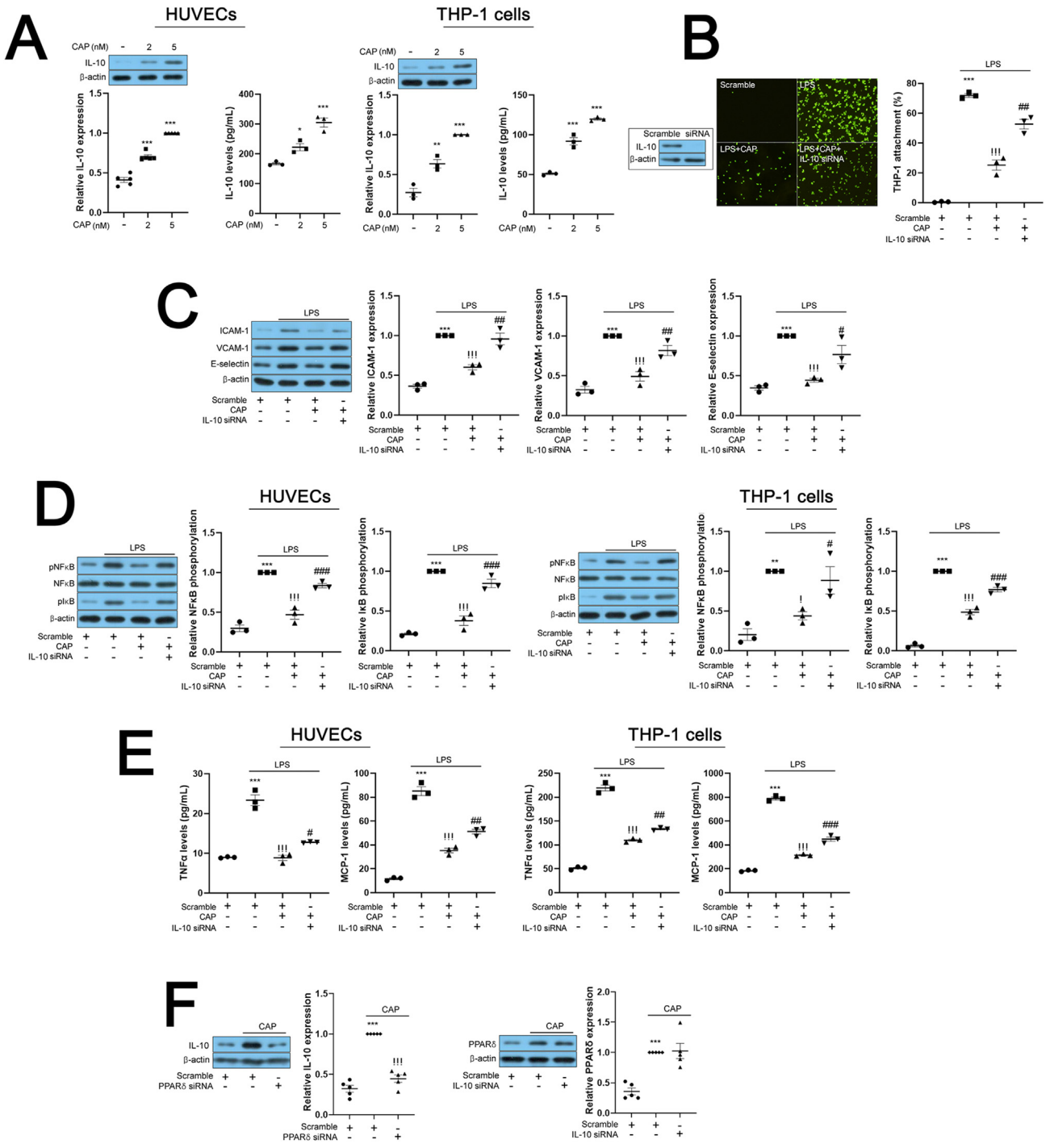

Fig. 4 **PPARδ/IL-10 pathway contributes to the suppressive effects of CAP on inflammation and adhesion between HUVECs and THP-1 cells.** (A) Western blot analysis of IL-10 in HUVECs and THP-1 cells treated with 0–5 nM CAP for 24 h. THP-1 cell adhesion assay (B) and Western blotting of ICAM-1, VCAM-1, and E-selectin (C) in scrambled or IL-10 siRNA (20 nM)-transfected HUVECs treated with LPS (200 ng/mL) and CAP (5 nM) for 24 h. (D) Western blot analysis of phosphorylated NFκB and IκB in scrambled or IL-10 siRNA (20 nM)-transfected HUVECs and THP-1 cells treated with LPS (200 ng/mL) and CAP (5 nM) for 24 h. (E) ELISA of TNFα and MCP-1 in culture media of scrambled or IL-10 siRNA (20 nM)-transfected HUVECs and THP-1 cells treated with LPS (200 ng/mL) and CAP (5 nM) for 24 h. (F) Western blotting of IL-10 in scrambled or PPARδ siRNA (20 nM)-transfected HUVECs and THP-1 cells treated with CAP (5 nM) for 24 h. Western blotting of PPARδ in scrambled or IL-10 siRNA (20 nM)-transfected HUVECs and THP-1 cells treated with CAP (5 nM) for 24 h $^{***}p < 0.001$ and $^{**}p < 0.01$ when compared to control. $^{!!!}p < 0.001$, $^{!!}p < 0.01$, and $^{!}p < 0.05$ when compared to LPS or CAP. $^{\#\#\#}p < 0.001$, $^{\#\#}p < 0.01$, and $^{\#}p < 0.05$ when compared to LPS plus CAP.

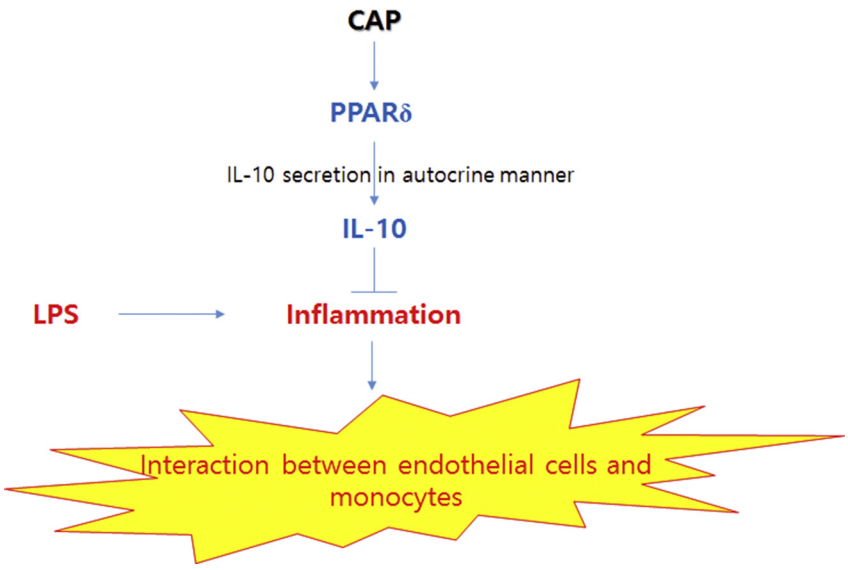

Fig. 5 **Schematic diagram of the effects of CAP on the adhesion between endothelial cells and monocytes, and its related pathways.**

PPARδ, a ligand-activated transcription factor, is a member of the nuclear hormone receptor superfamily [23]. It is essential for the control of cellular energy metabolism and inflammation [24]. In this context, Zingarelli et al. have found that PPARδ activation by a specific PPARδ ligand attenuates inflammation via suppression of NFκB-mediated pathway in sepsis models [25]. Telmisartan inhibits the pro-inflammatory effects of homocysteine on HUVECs via the PPARδ-dependent pathway [26]. Lee et al. have demonstrated that kynurenic acid alleviates inflammatory responses in HUVECs through PPARδ/heme oxygenase-1 (HO-1) signaling [17]. Therefore, these studies propose PPARδ as a therapeutic target for inflammatory metabolic diseases, including atherosclerosis [15]. We found that CAP treatment augmented PPAR expression in HUVECs and THP-1 monocytes in this investigation. Suppression of PPARδ expression by siRNA reduced the effects of CAP on LPS-mediated cell adhesion between HUVECs and THP-1 monocytes and inflammatory responses. These results denote that PPARδ contributes to the suppressive effects of CAP on LPS-induced monocyte-endothelial adhesion and inflammation in HUVECs and THP-1 monocytes.

IL-10, an anti-inflammatory cytokine, blocks the synthesis of pro-inflammatory cytokines in inflamed monocytes [27]. Several studies have shown that IL-10 has an anti-atherogenic property. For instance, recombinant IL-10 inhibits monocyte adherence to endothelial cells via suppression of cell adhesion molecules [28,29]. Recombinant IL-10 administration mitigated stent-implantation-mediated intimal hyperplasia in hypercholesterolemic animal models [30]. Conversely, IL-10-deficient mice demonstrated the development of severe atherosclerosis evidenced by increased T-cell infiltration and reduction of collagen content in atherosclerotic lesions [18]. The current study found that treating HUVECs and THP-1 monocytes with CAP increased cellular IL-10 expression and IL-10 release to culture media. Similar to PPARδ, IL-10 siRNA reduced the effects of CAP on HUVECs and THP-1 cells in the presence of LPS. Furthermore, siRNA for PPARδ mitigated CAP-induced IL-10 expression, whereas IL-10 siRNA did not influence the induction of PPARδ expression by CAP. These results indicate that the PPARδ-regulated IL-10 axis has an enormous impact on the effects of CAP on monocyte-endothelial adhesion and inflammation.

To summarize, we discovered that CAP improves inflammation via PPARδ/IL-10 signaling, thereby attenuating adhesion between HUVECs and THP-1 cells (Fig. 5). Hence, this study shows the potential of CAP as a treatment for atherosclerosis. Indeed, additional *in vivo* experiments using atherosclerotic animal models are needed to reinforce this conclusion.

CRediT author statement

Hyung Sub Park: Conceptualization; Investigation; Methodology. **Taeseung Lee:** Conceptualization; Investigation; Methodology. **Ji Hoon Jeong:** Conceptualization; Writing - original draft. **Tae Woo Jung:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Writing - original draft. **A. M. Abd El-Aty:** Writing - original draft; Writing - review & editing. All authors approved the final version of the manuscript. **Hyung Sub Park**, **Taeseung Lee**, and **Tae Woo Jung** are responsible for the overall integrity of the work.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2022.04.005.

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