Biochemical and Biophysical Research Communications 452 (2014) 998–1003

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Urotensin II increases foam cell formation by repressing ABCA1 expression through the ERK/NF-κB pathway in THP-1 macrophages

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ARTICLE INFO

Article history:
Received 3 September 2014
Available online 16 September 2014

Keywords:
Urotensin II
ERK
NF-κB
ABCA1
Cholesterol efflux

ABSTRACT

Objective: Foam cell formation in the arterial wall plays a key role in the development of atherosclerosis. Recent studies showed that Urotensin II (U II) is involved in the pathogenesis of atherosclerosis. Here we examined the effects of human U II on ATP-binding cassette transporter A1 (ABCA1) expression and the underlying mechanism in THP-1 macrophages.

Methods and results: Cultured THP-1 macrophages were treated with U II, followed by measuring the intracellular lipid contents, cholesterol efflux and ABCA1 levels. The results showed that U II dramatically decreased ABCA1 levels and impaired cholesterol efflux. However, the effects of U II on ABCA1 protein expression and cellular cholesterol efflux were partially reversed by inhibition of extracellular signal regulated kinase 1/2 (ERK1/2) and nuclear factor kappa B (NF-κB) activity, suggesting the potential roles of ERK1/2 and NF-κB in ABCA1 expression, respectively.

Conclusion: Our current data indicate that U II may have promoting effects on the progression of atherosclerosis, likely through suppressing ABCA1 expression via activation of the ERK/NF-κB pathway and reducing cholesterol efflux to promote macrophage foam cell formation.

1. Introduction

Hypertension, hyperlipidemia and hyperglycaemia are the risk factors of coronary heart disease, in which atherosclerosis, plays an important role in its onset and outcome. Macrophage foam cell formation in the arterial intima is a typical feature in the early stages of atherosclerotic lesions [1]. We and others have demonstrated that ATP-binding cassette transporter A1 (ABCA1) is a cholesterol transporter that transfers excess cellular cholesterol onto lipid-poor apolipoprotein AI (apoAI) and induces cholesterol and phospholipid efflux [2,3]. Down-regulation ABCA1 expression impairs apoAI-mediated lipid efflux from cells. ABCA1 knockout mice develop early atherosclerosis [4]. In clinical practice, some specific patients like those with Tangier disease and familial high density lipoprotein cholesterol (HDL-C) deficiency are characterized by very low levels of circulating HDL-C due to the mutations of functional ABCA1 [5,6]. Given the critical role of ABCA1 in cholesterol homeostasis, ABCA1 has become a therapeutic target for atherosclerosis.

Human urotensin II (U II) is one of the most potent vasoconstrictor peptide identified to date. It is expressed mainly in the cardiovascular system and involved in hypertension and atherosclerosis [7–9]. U II and its receptor system GPR14, an orphan G protein-coupled receptor, exert a series of biological effects, such as vascular contraction and mitogen effects [10–12]. Many studies have shown that U II plays an important role in the homeostatic regulation of cardiovascular system and the development of vascular disease. For example, U II regulates cholesterol metabolism by up-regulating the expression of Acyl-coenzyme A:cholesterol acyltransferase-1 (ACAT-1) expression, which converts intracellular free cholesterol into cholesterol ester (CE) for storage in lipid droplets, leading to the formation of monocyte-derived macrophage foam cells in atherosclerotic lesions [13]. Thus, it is potentially

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http://dx.doi.org/10.1016/j.bbrc.2014.09.030
0006-291X/

important and has clinical value to apply U II to prevent and/or treat atherosclerosis.

The regulation of ABCA1 at transcriptional and posttranscriptional levels has been well characterized [14–16]. Identification of a novel pathway that regulates ABCA1 expression may provide a new strategy to manage cholesterol metabolism. The previous study has revealed that U II induces interlukin-8 (IL-8) expression in human umbilical vein endothelial cells via p38 mitogen-activated protein kinase and extracellular signal-regulated kinase (ERK) signaling pathways [17]. Inhibition of ERK1/2 and activation of Liver X Receptor synergistically induce ABCA1 expression and macrophage cholesterol efflux, suggesting that ERK1/2 activity can play an important role in macrophage cholesterol trafficking [18]. U II also stimulates signal transduction pathways to lead to the long-lasting activation of ERK1/2 in Chinese hamster ovary cells expressing human GPR14 (CHO-GPR14), which may be involved in long-lasting physiological effects, such as the one on cardiovascular remodeling [19]. However, the interrelationship among U II, ABCA1 gene expression and cholesterol efflux in THP-1 macrophage has not been studied. This study aimed to define the molecular mechanisms underlying U II regulation of ABCA1 expression in THP-1 macrophages. Our studies herein revealed that the intracellular signal transduction pathway through which U II suppresses ABCA1 expression involves the ERK/NF-κB cascade in THP-1 macrophages and cholesterol trafficking process.

2. Materials and methods

2.1. Reagents and antibodies

RPMI medium 1640 was obtained from Solarbio (Beijing, China). Fetal bovine serum (FBS) was purchased from Invitrogen (Carlsbad, CA). U II was from Westang (Shanghai, China). Rabbit anti-total ERK1/2 and 1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylmercapto)butadiene (U0126) were purchased from Cell Signaling Technology (Beverly, MA). NF-κB inhibitor Pyrrolidine dithiocarbamic acid (PDTC) and antibodies for phosphorylated proteins were obtained from Sigma–Aldrich (California, USA). [^{3}H] Cholesterol and phorbol-12-myristate-13-acetate (PMA) were purchased from Sigma–Aldrich (St Louis, MO). Oxidized low-density lipoprotein (ox-LDL) was prepared as described previously [20]. Mouse monoclonal antibody to ABCA1 was from Abcam (Cambridge, United Kingdom).

2.2. Cell culture and treatment

Human THP-1 cells were purchased from the Institute of Cell Biology of the Cell Center (Shanghai, China). Cells were cultured as previously described [21,22]. After 3–4 d, cells were treated with PMA (160 nmol/L) for 24 h to be differentiated into macrophages. The medium was then replaced with serum-free medium containing ox-LDL (50 μg/mL) for 48 h so as to let cells transform into foam cells for the subsequent experiments. The cells were then fixed with 4% paraformaldehyde, followed by staining with 0.5% Oil red O dye. Cells were counterstained with hematoxylin and photographed at ×40 magnification.

2.3. Cholesterol efflux experiments

Cells were cultured as indicated above, followed by labeling with 0.2 μCi/mL of [^{3}H] cholesterol. After 72 h, cells were washed with PBS and incubated with RPMI 1640 medium containing 0.1% (wt/vol) bovine serum albumin (BSA) overnight to allow equilibration of [^{3}H] cholesterol in all cellular pools. Cells were then washed with PBS and incubated in 2 mL of efflux medium containing RPMI 1640 medium and 0.1% BSA. Medium- and cell-associated [^{3}H] cholesterols were then measured by liquid scintillation counting. Percent efflux was calculated by the following equation: [total media counts/(total cellular counts + total media counts)] × 100%.

2.4. High performance liquid chromatography (HPLC) assay

The sterol analyses were performed using a high performance liquid chromatography (HPLC) system (model 2790, controlled with Empower Pro software; Waters Corp, Milford, MA, USA). HPLC analysis was conducted as previously described [23,24]. Data were analyzed with Total Chrom software from PerkinElmer.

2.5. Western blot analysis

Western blot analysis was performed as described before [21]. Cell proteins (20 μg each) were loaded on 8% sodium-dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) and electrophoresed for 2 h at 100 V in the buffer containing 25 mM Tris base, 250 mM glycine, and 0.1% SDS. The protein samples were visualized using a chemiluminescence method (ECL Plus Western Blotting Detection System; Amersham Biosciences).

2.6. RNA isolation and real-time quantitative polymerase chain reaction (RT-qPCR) analysis

Total RNA was isolated from cultured THP-1 macrophages using the RNeasy Minikit (Qiagen, Valencia, CA) according to the manufacturer's instructions. RT-qPCR assays were performed as previously described [25]. Melt curve analyses of all RT-qPCR products were performed and shown to produce a single DNA duplex. Quantitative measurements were determined using the $^{\Delta\Delta}$Ct method, and the expression of β-actin was used as the internal control.

2.7. Statistical analysis

All data are presented as means ± standard deviations (SDs). Results were analyzed by one-way analysis of variance and Student's *t* test. Statistical analyses were conducted with SPSS 13.0 software, and p-values < 0.05 were considered statistically significant.

3. Results

3.1. U II decreases ABCA1 expression in THP-1 macrophages

To investigate the effects of U II on foam cell formation, we first examined the effect of U II on ABCA1 expression. THP-1 macrophages were treated with various concentrations of U II (0–30 nmol/L) as indicated for 24 h or incubated with 20 nmol/L of U II for different time points. RT-qPCR and western blot analyses were performed to measure ABCA1 mRNA abundance and protein levels, respectively. Our results revealed the concentration-dependent effects of U II on ABCA1 expression in THP-1 macrophages (Fig. 1A and B). U II decreased ABCA1 protein and mRNA expression in a concentration-dependent manner with the maximal effect observed at the concentration of 20 nmol/L. The time course studies showed similar effects of U II (20 nmol/L) on ABCA1 expression (Fig. 1C and D). These results indicate that U II reduced ABCA1 expression at both transcriptional and translational levels in both concentration- and time-dependent manner.

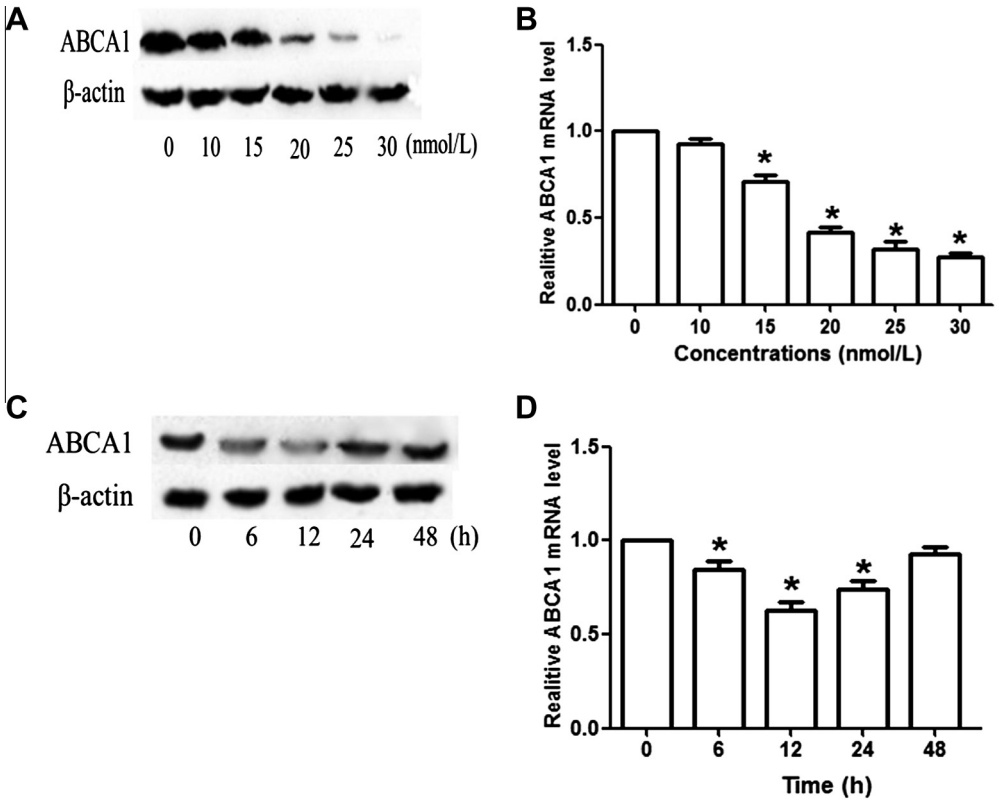

Fig. 1. U II decreases ABCA1 expression in THP-1 macrophages. Cells were treated with various concentrations of U II as indicated for 24 h (A and B) or incubated with 20 nmol/L U II for various time periods (C and D). (A and C) Effects of U II on ABCA1 protein expression. Total proteins were extracted from cells with various treatments. The protein levels of ABCA1 or β-actin were measured by western blot assay. (B and D) Effects of U II on ABCA1 mRNA levels. Total RNA was extracted, followed by RT-qPCR as described in Section 2. All results are expressed as mean ± SD from three independent experiments with each performed in triplicate. $^{*}P < 0.05$ vs. control.

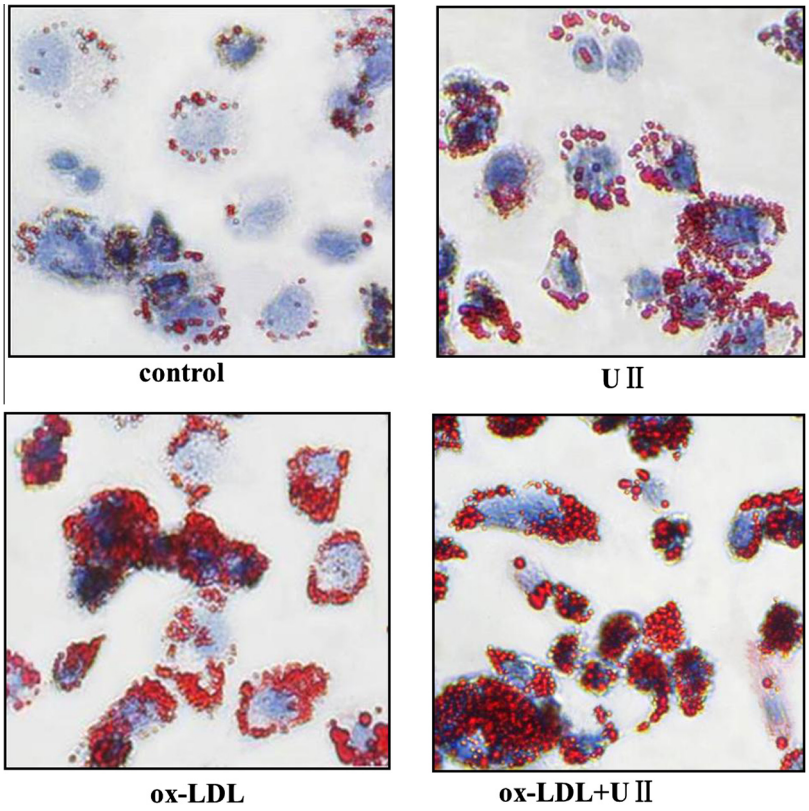

Fig. 2. U II induces cholesterol accumulation in THP-1 macrophages. THP-1 cells were incubated with U II (20 nmol/L) for 24 h, followed by fixation and staining with Oil red O dye. The magnification of each panel is ×40 (A). ox-LDL, oxidized low-density lipoprotein.

Table 1
Concentration-dependent effects of U II on cholesterol content in THP-1 macrophages. THP-1 macrophages were divided into 6 groups and cultured in medium at 37 °C containing different concentrations of U II. HPLC was then performed to determine the levels of cellular total cholesterol (TC), free cholesterol (FC) and cholesterol ester (CE).

	U II (nmol/L)					
	0	10	15	20	25	30
TC (μg/mg)	320 ± 27	390 ± 21	421 ± 33	486 ± 35*	490 ± 29*	483 ± 25*
FC (μg/mg)	173 ± 19	194 ± 24	208 ± 28*	192 ± 37*	195 ± 31*	189 ± 22*
CE (μg/mg)	147 ± 28	196 ± 24	213 ± 27	294 ± 19*	295 ± 26*	294 ± 21*
CE/TC (%)	46.2	50.1	50.7	60.6	60.3	60.9

Values represent the mean ± SD from three independent experiments.
* $P < 0.05$ vs. control.

3.2. U II induces cholesterol accumulation in THP-1 macrophages

In coronary arteries, the development of atherosclerotic lesions is an underlying cause of coronary heart disease [26]. Given that lipid-laden macrophage/foam cells are a prominent part of atherosclerotic lesion, we examined the regulatory effect of U II on cholesterol content in THP-1 macrophages. Our results obtained from Oil red O staining showed that U II treatment markedly increased cellular lipid accumulation (Fig. 2). HPLC was then conducted to determine cellular cholesterol content. As shown in Tables 1 and 2, cellular cholesterol contents were increased when THP-1 macrophages were treated with U II.

3.3. U II blocks cholesterol efflux in ox-LDL-treated THP-1 macrophages

ABCA1 is a key player in reverse cholesterol transport and critically regulates cellular cholesterol homeostasis [27–29].

Table 2
Concentration-dependent effects of U II on cholesterol content in THP-1 macrophages. THP-1 macrophages were divided into 5 groups and cultured in medium at 37 °C containing 20 nmol/L of U II for different time periods as indicated. HPLC was then performed to determine the levels of cellular total cholesterol (TC), free cholesterol (FC) and cholesterol ester (CE).

	Time (h)				
	0	6	12	24	48
TC (μg/mg)	298 ± 41	361 ± 36*	496 ± 34*	385 ± 28*	223 ± 26
FC (μg/mg)	139 ± 27	144 ± 21	194 ± 20*	156 ± 19*	91 ± 16
CE (μg/mg)	159 ± 22	217 ± 19*	302 ± 27*	229 ± 26*	132 ± 17
CE/TC (%)	53.4	60.3	60.9	59.5	59.2

Values represent the mean ± SD from three independent experiments.
* $P < 0.05$ vs. control.

Therefore, we also examined the effects of U II on apoAI-mediated cholesterol efflux in THP-1 macrophages using liquid scintillation counting assays. Our results showed that apoAI-mediated cholesterol efflux was decreased when cells were treated with U II (Fig. 3A and B), which inhibition likely results from the reduced expression of ABCA1 in THP-1 macrophages.

3.4. ERK/NF-κB pathway in U II-induced inhibitory of ABCA1 expression

Several signaling pathways have been implicated in the induction of ABCA1 expression. To test the possibility of the ERK/NF-κB pathway in U II-induced down-regulation of ABCA1 expression in THP-1 macrophages, we firstly treated the cells with U0126, an chemical inhibitor of ERK1/2, or PDTC, an inhibitor of NF-κB to inhibit ERK and NF-κB signaling pathways, respectively. After 24 h treatment, ABCA1 protein and mRNA levels were analyzed by western blotting (Fig. 4A) and RT-qPCR assays (Fig. 4C), respectively. As expected, our results showed that inhibition of ERK1/2 by U0126 suppressed U II-induced increase in NF-κB phosphorylation (Fig. 4B). In addition, the inhibitory effects of U II on ABCA1 expression was partially reversed by the two inhibitors. Taken together, these data suggest that U II may activate ERK1/2, and subsequently phosphorylate NF-κB, which then translocates to the nucleus and directly or indirectly exerts its inhibitory effects on ABCA1 gene transcription.

4. Discussion

Increasing evidence suggests a reciprocal relationship between atherosclerotic heart disease and hypertension. Human U II is a vasoactive peptide identified in vascular and cardiac tissues (including coronary atheroma). It exerts contractile effects on

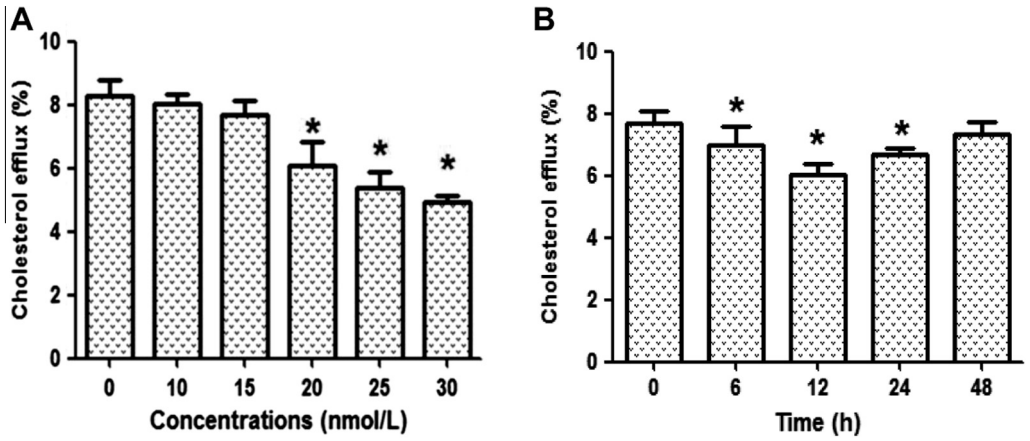

Fig. 3. U II blocks cholesterol efflux in ox-LDL-treated THP-1 macrophages. Concentration- and time-dependent effects of U II on cholesterol efflux in THP-1 macrophages. The cells were incubated with different concentrations of U II as indicated for 24 h (A) or with 20 nmol/Lof U II for indicated times (B). Then cholesterol efflux was analyzed by liquid scintillation counting assays as described in Section 2. The results are expressed as mean ± SD from three independent experiments with each performed in triplicate. *$P < 0.05$ vs. control.

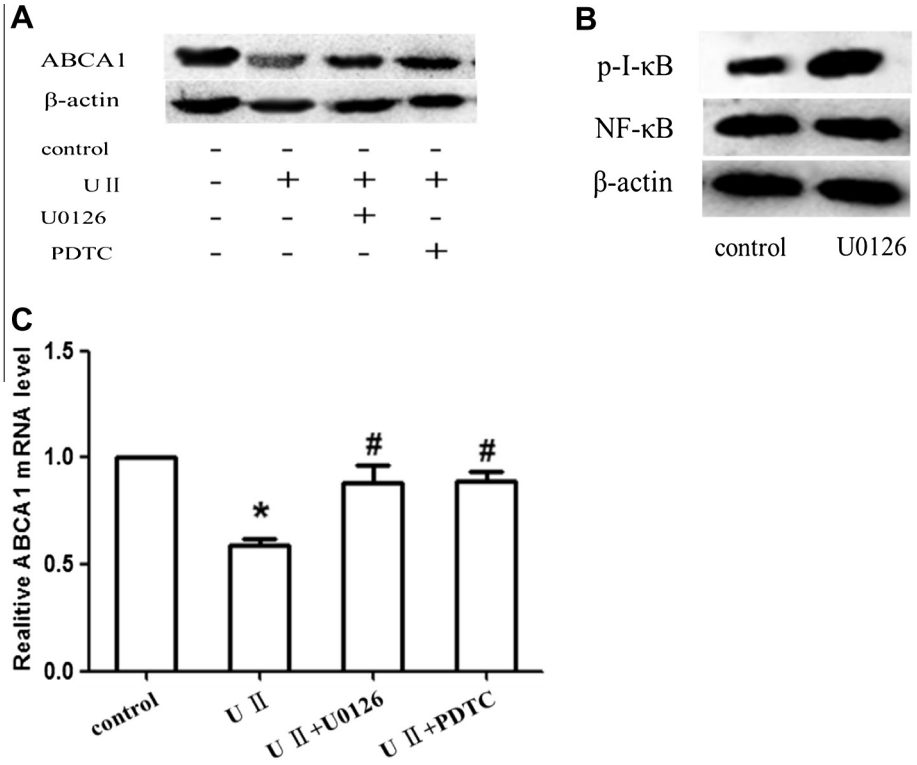

Fig. 4. ERK/NF-κB pathway in U II-induced down-regulation of ABCA1. Cells were treated without (control) and with U0126, PDTC for 30 min, followed by treatment with 20 nmol/L of U II for the indicated time periods. ABCA1 and NF-κB (p-NF-κB) protein levels were determined by western blot analysis (A and B). Total ABCA1 mRNA (C) levels were determined by RT-qPCR and normalized to β-actin. Values represent the mean ± SD from three independent experiments with each performed in triplicate. $^{*}P < 0.05$ vs. control, $^{\#}P < 0.05$ vs. U II group.

arteries from nonhuman primates, including coronary, pulmonary and carotid arteries, suggesting its role in the development of hypertension [7]. Recently, there is an increased concern about the impact of U II on atherosclerosis. Plasma U II levels elevate in patients with acute coronary syndrome (ACS), particularly right after their clinical presentation [30]. Bousette et al. previously showed that U II and U II receptor mRNA were detected in lymphocytes and monocytes/macrophages isolated from human peripheral blood mononuclear cells of healthy subjects, respectively, and U II immunoreactivity was found in the regions infiltrated with macrophages within atherosclerotic lesions [9,31]. These findings suggest that U II could attract blood monocytes expressing the U II receptor to inflammatory sites, and also reinforce the idea that U II may play a critical role in the pathogenesis of atherosclerosis [32].

Cellular cholesterol content in macrophages is determined by uptake and efflux of cholesterol. ABCA1, ATP-binding cassette transporter G1 (ABCG1) and scavenger receptor class B, type I (SR-BI) are cholesterol transporters to promote efflux of excess cholesterol from macrophages and then transport it back to the liver for excretion into the bile and eventually the feces *in vivo* [33]. In the present study, we sought to determine the effects of U II on ABCA1 expression in THP-1 macrophages and the underlying mechanism. THP-1 macrophages were treated with different concentrations of U II, followed by measuring the ABCA1 expression using western blotting and RT-qPCR assays. The results revealed that inhibitory effects of U II on ABCA1 protein and mRNA levels are both concentration- and time-dependent. The early lesions of atherosclerosis consist of subendothelial accumulation of cholesterol-engorged macrophages, which are called foam cells. Notably, foam cells produce various bioactive molecules, such as growth differentiation factor-15, which could enhance cholesterol efflux through increasing membrane-associated ABCA1 protein level [34]. Moveover, we revealed the effects of U II on macrophage-derived foam cell formation. Our Oil red O staining results showed that treatment with U II significantly increased cellular lipid accumulation. Using liquid scintillation counting assays, we observed that the efflux of radioactive cholesterol from the cells was also decreased. strongly suggesting that U II may contribute to foam cell formation through decreasing ABCA1 expression and attenuating the cellular cholesterol efflux.

Defects in ABCA1 lead to Tangier disease and familial hypoalphalipoproteinemia, characterized by very low levels of plasma HDL-C [5]. It is well known that HDL prevents CHD primarily by removing excess cholesterol from arterial macrophages and transporting it back to the liver [35]. The first step of this pathway, called reverse cholesterol transport, is mediated by ABCA1. Thus, targeting ABCA1 receptor-like property using agonists for ABCA1 protein could become a promising new therapeutic approach to increase ABCA1 function and treat cardiovascular disease. Importantly, the results from our experiments have provided further supporting evidence to this concept from the opposite side. Our results demonstrated that U II down-regulates ABCA1 expression via the ERK/NF-κB signaling pathway, resulting in cholesterol accumulation, particularly cholesterol ester in THP-1 macrophages. However, treatment of cells with U0126, an chemical inhibitor of ERK, or PDTC, an inhibitor of NF-κB inhibited the ERK/NF-κB signaling pathway and, partially reversed U II-induced down-regulation of ABCA1 expression. Therefore, we conclude that U II stimulates ERK1/2 and subsequently the NF-κB pathway, which then reduces the expression of ABCA1. This effect of U II, to a certain extent, accelerates the formation of macrophage-derived foam cells, likely contributing to the pathogenesis of atherosclerosis.

Acknowledgments

The authors gratefully acknowledge the financial support from the National Natural Sciences Foundation of China (81170278 and 81370377). Aid Program for Science and Technology Innovative Research Team in Higher Educational Institutions of Hunan Province (2008-244) and the construct program of the key discipline in Hunan Province, China.

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