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L-Cysteine-induced up-regulation of the low-density lipoprotein receptor is mediated via a transforming growth factor-alpha signalling pathway

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ABSTRACT

Sulphur-containing amino acids regulate plasma cholesterol levels in animals and humans. However, their mechanism of action remains unclear. Low-density lipoprotein receptor (LDLR) plays an important role in cholesterol metabolism. We therefore investigated the effects of sulphur-containing amino acids on the expression of LDLR in hepatocytes. HepG2 cells were cultured in Dulbecco's Modified Eagle's Medium with or without sulphur-containing amino acids and cysteine-containing compounds. We found that L-cysteine increased LDLR mRNA and enhanced LDLR gene promoter activity through the extracellular-signal-related kinase and p38 mitogen-activated protein kinase signalling pathways in HepG2 cells. Moreover, we observed that L-cysteine stimulated the release of transforming growth factor-alpha (TGF-α) and that TGF-α increased the LDLR mRNA levels. This study provides a report of the L-cysteine mediated up-regulation of the LDLR expression via TGF-α signalling pathway. Our findings provide insights into cholesterol homeostasis and amino acid signalling.

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1. Introduction

Atherosclerosis is a serious risk factor for cardiovascular disease, which is one of the leading causes of morbidity and mortality worldwide [1]. Increased levels of blood lipids, especially low-density lipoprotein (LDL) cholesterol, are major risk factors for atherosclerosis [2]. Since most of the plasma LDL cholesterol is removed by the liver through LDL receptor (LDLR)-mediated uptake [3]. Inducing the expression of LDLR in the liver can be an effective strategy for preventing atherosclerosis.

Regulation of LDLR expression is known to occur at the transcriptional, post-transcriptional, and post-translational levels [4–6]. The transcriptional regulation of the LDLR gene is mediated by one of the sterol regulatory element binding proteins (SREBPs), which are transcription factors [7,8]. The protein level of LDLR is regulated by proprotein convertase subtilisin/kexin type 9 (PCSK9) [9,10]. The mechanisms underlying the post-transcriptional regulation of LDLR mRNA remain unknown, but one aspect that is known is the modulation of LDLR mRNA stability by a group of AU-rich element (ARE) binding proteins [11].

Of the amino acids, the only ones that contain sulphur are L-methionine and L-cysteine. L-Methionine is an essential amino acid that is metabolized to L-cysteine. L-Cysteine is the precursor of glutathione (GSH), which is a major antioxidant in mammals. Both amino acids play an important role in protein synthesis. Although 75% of dietary L-cysteine is absorbed in the intestine, only 25% of the absorbed L-cysteine is utilised in the intestine itself [12], while most of the L-cysteine is generally metabolised in the liver [13]. L-Cysteine has several physiological functions. For example, L-cysteine restores biochemical lesions caused by excessive ingestion of trace elements such as copper, cobalt, and selenium via chelation reactions [14]. Interestingly, a study reported that a meal free of sulphur-containing amino acids increased plasma lipids in humans [15]. L-Cysteine, cysteine-containing compounds, including *N*-acetyl-L-cysteine (NAC) and *S*-methyl-L-cysteine sulphoxide (SMCS), and taurine have also been reported to affect lipid metabolism [16–20]. Moreover, a significant negative correlation has been reported between blood cholesterol concentrations and the level of cystine in intact dietary proteins for these sulphur-containing amino acids [20]. However, the mechanism of action of these sulphur-containing amino acids remains unknown.

In the present study, we examined the effects of sulphur-containing amino acids and cysteine-containing compounds on

Abbreviations: ERK, extracellular-signal-related kinase; MAPK, mitogen-activated protein kinase.

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cholesterol metabolism-related genes in hepatocytes. Moreover, we provided insight into the mechanism of how L-cysteine induced up-regulation of LDLR in hepatocytes.

2. Materials and methods

2.1. Materials

L-Cysteine, L-methionine, taurine, and SB203580 were purchased from Sigma. NAC, U0126, and TGF-α were obtained from Wako. SMCS was purchased from Research Organics. SP600125 was obtained from Merck. Unless otherwise indicated, all other chemicals were purchased from Sigma or Wako and were guaranteed to be reagent or tissue culture grade.

2.2. Cell culture

HepG2 (EC85011430), the human hepatoblastoma cell line, was obtained from European Collection of Cell Cultures (ECACC) and was cultured in Dulbecco's Modified Eagle's Medium (DMEM; MP Biomedicals, Japan) containing 10% charcoal/dextran-treated foetal bovine serum (FBS), 100 U/ml penicillin, 100 μg/ml streptomycin, and 10 mM of a non-essential amino acids solution (Invitrogen) at 37 °C in a humidified O_2/CO_2 (19:1) atmosphere.

2.3. RNA preparation and quantitative real-time PCR analysis

RNA preparation and quantitative real-time PCR were performed as described previously [21]. The primers and TaqMan® probes for human LDLR (Hs00181192 m1), cholesterol 7α-hydroxylase (CYP7A1; Hs00167982 m1), hydroxymethylglutaryl-CoA (HMG-CoA) reductase (Hs00168352 m1), and SREBP-2 (Hs01081784 m1) were purchased from Applied Biosystems as part of the TaqMan® Gene Expression Assay. The mRNA expression levels of the target genes were standardised against 18S ribosomal RNA.

2.4. Transient transfections and luciferase assay

A reporter plasmid for LDLR was gifted from the Osaka University [22]. HepG2 cells were transfected with 1.5 μg of human LDLR-Luc plasmid (pGL4.10-Luc) containing the promoter region (−4000 to +57 bp) of the human LDLR gene and 0.5 μg pPGK β-galactosidase plasmid as an internal control. Transfection was allowed to proceed for 5 h in serum-free Opti-MEM I (Gibco) using Lipofectin Reagent (Invitrogen). After the transfection, cells were incubated with 10 mM L-cysteine for 12 h. The cells were then lysed with Reporter Lysis Buffer (Promega). Luciferase activity was measured using a Luciferase Assay System (Promega) and Fluoroskan Ascent FL (Labsystems) according to the manufacturer's instructions. β-Galactosidase activity was measured using a β-Gal ELISA kit (Promega).

2.5. TGF-α ELISA

Cell culture medium was collected after treatment with L-cysteine, and then, TGF-α levels were measured using the Human TGF-α Immunoassay Kit (R&D Systems), according to the manufacturer's protocol.

2.6. Statistical analysis

The results are expressed as mean ± SEM. The statistical significance of the differences was evaluated using the Student's *t* test [23] and Tukey's test [24]. Differences were considered significant when $P < 0.05$.

3. Results

3.1. The effects of L-cysteine and cysteine-containing compounds on the expression of cholesterol metabolism-related genes

To investigate the effect of L-cysteine, L-methionine, taurine, NAC, or SMCS on the expression of cholesterol metabolism-related

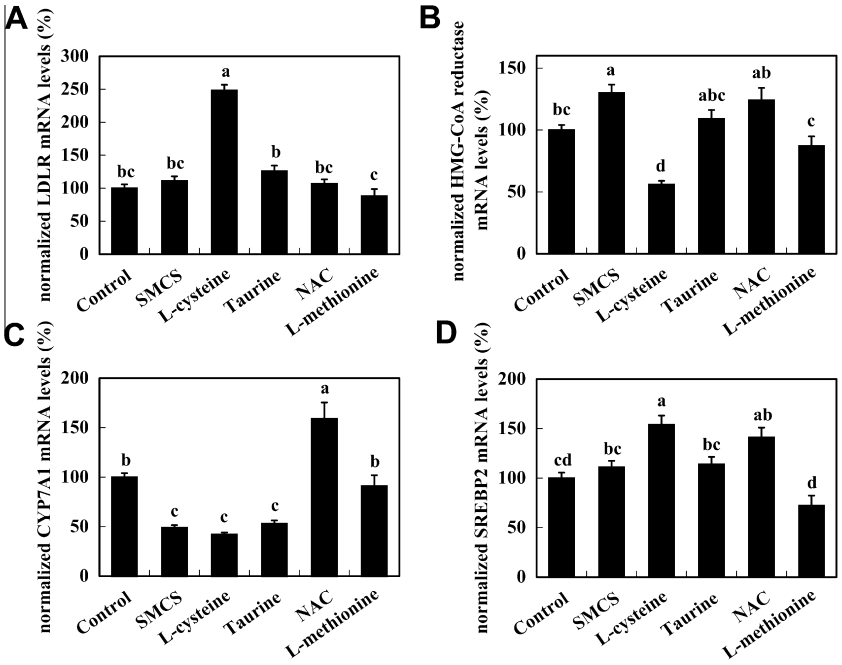

Fig. 1. Effect of L-cysteine, L-methionine, SMCS, taurine, or NAC on the levels of (A) LDLR, (B) HMG-CoA reductase, (C) CYP7A1, and (D) SREBP2 mRNA expression. Cells were incubated in FBS-free medium with or without compounds. Total RNA was prepared from HepG2 cells treated with vehicle control, 10 mM L-cysteine, L-methionine, SMCS, taurine, or NAC for 24 h. Relative mRNA levels were determined by quantitative real-time PCR analysis after normalisation to 18S ribosomal RNA. The data are shown as mean ± SEM ($n = 6$). Different superscripts indicate significantly different values ($P < 0.05$) by Tukey's test.

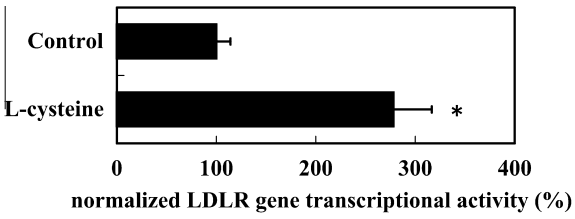

Fig. 2. Effect of L-cysteine on LDLR gene transcriptional activity. HepG2 cells were transfected with human LDLR-Luc plasmid (pGL4.10-Luc), using the pPGK β-galactosidase plasmid as an internal control. After transfection, the cells were treated with 10 mM L-cysteine for 12 h. Data are presented as luciferase activity normalised to β-galactosidase activity. The data are shown as mean ± SEM (n = 5 or 6). An asterisk indicates a significant difference from control cells by Student's t test ($P < 0.01$).

genes in hepatocytes, we performed quantitative real-time PCR analysis. HepG2 cells were treated with L-cysteine, L-methionine, taurine, NAC, or SMCS at a concentration of 10 mM for 24 h. We then investigated whether these compounds affected the mRNA levels of LDLR, CYP7A1, HMG-CoA reductase, and SREBP-2. The addition of L-cysteine significantly increased the mRNA level of LDLR (Fig. 1A). In contrast, CYP7A1 mRNA levels were significantly decreased by addition of SMCS, L-cysteine, and taurine, and were significantly increased by NAC (Fig. 1B). As shown in Fig. 1C, HMG-CoA reductase mRNA levels were markedly decreased by L-cysteine and were significantly increased by SMCS. Moreover, neither L-cysteine nor NAC significantly increased SREBP-2 mRNA levels (Fig. 1D). We also confirmed that these compounds were not cytotoxic to HepG2 cells at this concentration (incubation for 24 h; data not shown).

3.2. L-Cysteine affects the LDLR gene promoter activity

Next, we investigated the effect of L-cysteine on the LDLR gene promoter activity. HepG2 cells were treated with 10 mM L-cysteine for 12 h, and the cell lysates were subjected to luciferase assay. As shown in Fig. 2, treatment with 10 mM L-cysteine significantly increased LDLR promoter transcriptional activity by approximately 2.8-fold as compared with untreated cells.

3.3. ERK and p38 MAPK pathways mediates the L-cysteine induced increase in LDLR mRNA levels

To determine whether the up-regulation of LDLR by L-cysteine involved the mitogen-activated protein kinase (MAPK) signalling pathway, we next used the extracellular-signal-related kinase (ERK) inhibitor U0126, p38 MAPK inhibitor SB203580, and c-jun N-terminal kinase (JNK) inhibitor SP600125. We then performed quantitative real-time PCR analysis to investigate whether inhibition of MAPK signalling pathway affected LDLR mRNA levels. As shown in Fig. 3, the effect of L-cysteine on LDLR mRNA levels was blocked by using U0126 or SB203580.

3.4. L-Cysteine induces LDLR up-regulation via the TGF-α signalling pathway

Since TGF-α is known to be an ERK pathway activator, we next examined whether TGF-α was involved in the up-regulation of LDLR by L-cysteine. After HepG2 cells treated with 10 mM L-cysteine for 24 h, we measured TGF-α protein levels in the cell culture medium. TGF-α protein levels were significantly increased by treatment with L-cysteine (Fig. 4A). Moreover, after HepG2 cells

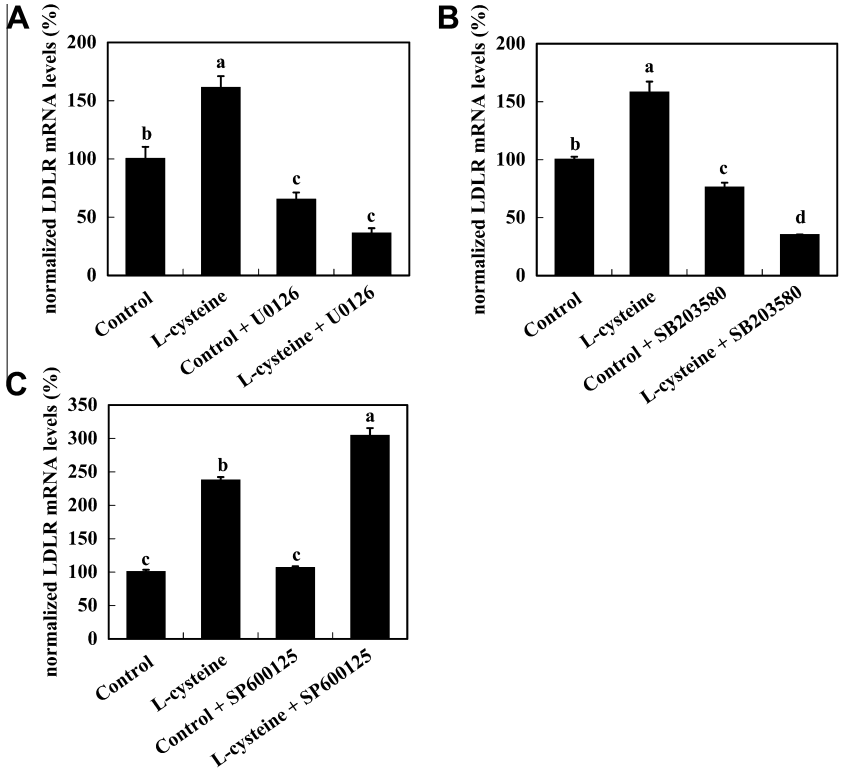

Fig. 3. Effect of L-cysteine on the levels of LDLR mRNA expression in HepG2 cells via MAPK signalling pathway. Cells were incubated in FBS-free medium with or without compounds. Total RNA was prepared from HepG2 cells treated (A) with vehicle control, 10 mM L-cysteine, 0.5 μM U0126, or 10 mM L-cysteine and 0.5 μM U0126 for 24 h, (B) with vehicle control, 10 mM L-cysteine, 30 μM SB203580, or 10 mM L-cysteine and 30 μM SB203580 for 24 h. (C) HepG2 cells were pretreated with 30 μM SP600125 for 3 h, then the cells were treated with 10 mM L-cysteine for 24 h. Relative mRNA levels were determined by quantitative real-time PCR analysis after normalisation to 18s ribosomal RNA. The data are the means ± SEM (n = 6). Different superscripts indicate significantly different values ($P < 0.05$) by Tukey's test.

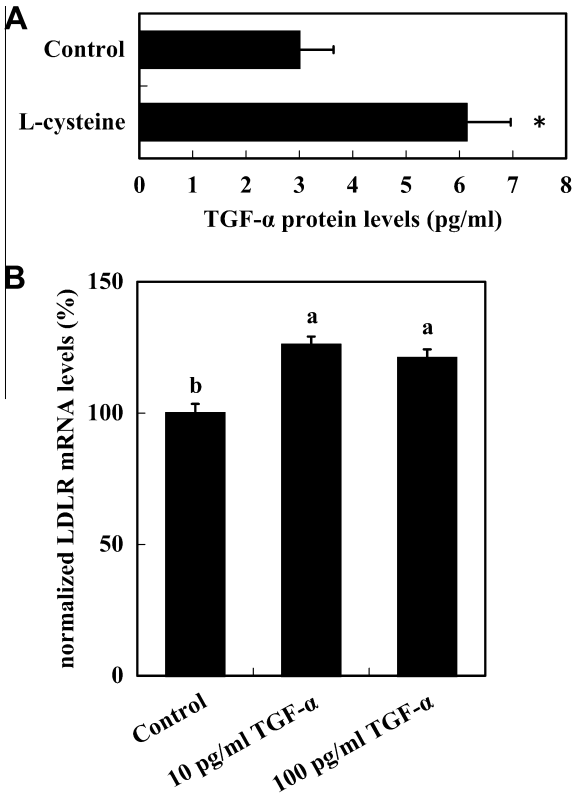

Fig. 4. TGF-α mediates the induction of LDLR expression by L-cysteine in HepG2 cells. Cells were incubated in FBS-free medium with or without compounds. (A) Cell culture medium was collected from HepG2 cells treated with vehicle control or 10 mM L-cysteine for 24 h. TGF-α protein levels were determined by TGF-α ELISA, with normalisation to total medium protein levels by Bradford protein assay. The data are presented as mean ± SEM ($n = 4$ or 5). An asterisk indicates a significant difference from control cells by Student's t test ($P < 0.05$). (B) Total RNA was prepared from HepG2 cells treated with vehicle control, 10 pg/ml TGF-α, or 100 pg/ml TGF-α for 24 h. Relative mRNA levels were determined by quantitative real-time PCR analysis after normalisation to 18S ribosomal RNA. The data are presented as mean ± SEM ($n = 6$). Different superscripts indicate significantly different values ($P < 0.05$) by Tukey's test.

were treated with 10 or 100 pg/ml TGF-α for 24 h, we performed quantitative real-time PCR analysis to investigate whether exposing HepG2 cells to TGF-α affected LDLR mRNA levels. As shown in Fig. 4B, treatment with 10 or 100 pg/ml TGF-α significantly increased LDLR mRNA levels.

4. Discussion

In this study, we investigated the effects of L-cysteine, L-methionine, taurine, NAC, and SMCS on LDLR, CYP7A1, HMG-CoA, and SREBP2 mRNA levels in HepG2 cells. HepG2 cells are extensively used in the metabolic studies of lipoprotein and cholesterol [25]. We report that all the compounds that we tested affected the expression of at least one of the target genes. In a recent study, it was reported that meals that were free from the sulphur-containing amino acids, namely, L-methionine and L-cysteine, increased plasma lipids in humans [15]. In our results, among the 5 compounds used in our experiments, L-cysteine caused a remarkable increase in LDLR mRNA levels, although L-methionine did not show any noticeable effect. Therefore, these results suggest that L-cysteine may decrease plasma lipids in humans.

Although we showed that L-cysteine up-regulates LDLR mRNA expression, its mechanism of action was not clear. Therefore, we tested the effect of L-cysteine on the transcription of the LDLR gene. L-Cysteine significantly activated LDLR promoter activity. In a recent study, it was reported that the amino acid glutamine up-regulated hepatic LDLR expression via the stimulation of SREBP processing [26]. In this study, we showed that L-cysteine up-regulated SREBP2 mRNA levels. Hepatic LDLR expression is known to be regulated mainly at the transcriptional level through the sterol regulatory element (SRE), which is the binding site for SREBP at the LDLR promoter [7,8]. Thus, the activation of LDLR gene transcription by L-cysteine may involve SREBP.

LDLR transcription is induced by various stimuli that cause the initiation of intracellular signalling events [27–30]. Interestingly, a recent study reported that cysteine/cystine redox induced activation of the ERK pathway via epidermal growth factor receptor (EGFR) signalling mediated by TGF-α [31]. TGF-α acts as a strong mitogen and is expressed in multiple cell types such as epithelial cells [32], keratinocytes [33], and macrophages [34]. TGF-α has approximately 30% structural homology with EGF and plays an important role in EGFR phosphorylation [35]. In this study, we showed that the up-regulation of LDLR by L-cysteine involved the ERK and p38 MAPK pathways. In addition, we observed that the level of TGF-α protein in the cell culture medium was increased by treatment with L-cysteine. Moreover, we demonstrated that exposing HepG2 cells to TGF-α significantly increased the LDLR mRNA levels. These results show that L-cysteine up-regulates LDLR expression via activation of the ERK and p38 MAPK signalling pathways mediated by TGF-α. TGF-α is synthesized as transmembrane pro-TGF-α, which is cleaved by metalloproteases and released as mature TGF-α [36]. Tumour necrosis factor alpha-converting enzyme (TACE), which is a member of the ADAM (a disintegrin and metalloproteinase) protein family and is called ADAM17, cleaves pro-TGF-α into mature TGF-α [37,38]. Activation of ADAMs is regulated by various kinases, which are activated by G protein-coupled receptors (GPCRs) [39,40]. Thus, interestingly, it is possible that L-cysteine mediates the cleavage of pro-TGF-α into mature TGF-α by TACE induced by the activation of GPCRs. We are currently trying to identify which GPCR mediates L-cysteine-induced LDLR up-regulation via the TGF-α signalling pathway.

Berberine is known to mediate the increase of LDLR mRNA expression, and previously, it was reported that the ERK pathway was required for the stabilising effect of berberine on LDLR mRNA [41]. Thus, L-cysteine may induce not only the activation of LDLR gene transcription but also the stabilisation of LDLR mRNA through the TGF-α signalling pathway.

In conclusion, our findings comprise a report that L-cysteine up-regulates the LDLR mRNA expression at the transcriptional level via the activation of ERK and p38 MAPK signalling pathways by TGF-α. Our findings provide insights into cholesterol homeostasis and amino acid signalling, and may lead to a strategy for improving lipid metabolism involved in hypercholesterolaemia and atherosclerosis.

Acknowledgments

Satoshi Nagaoka is the principal investigator who provided financial and idea leadership, designed and discussed experiments, supervised progress and direction of the study, edited and communicated the paper. Yuma Tanaka performed and analysed all the experiments, edited the paper. Masaya Shimada analysed the data, edited the paper. All authors read and approved the final paper. None of the authors has any conflicts of interest.

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