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HDL inhibit endoplasmic reticulum stress by stimulating apoE and CETP secretion from lipid-loaded macrophages

Loredan S. Niculescu [a,b], Gabriela M. Sanda [a], Anca V. Sima [a,*]

[a] Institute of Cellular Biology and Pathology "N. Simionescu" of the Romanian Academy, Bucharest, Romania
[b] National Institute for Economic Research "C.C. Kiritescu", Bucharest, Romania

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ABSTRACT

The role of HDL in the modulation of endoplasmic reticulum (ER) stress in macrophage-derived foam cells is not completely understood. Therefore, we aimed to investigate whether HDL may inhibit ER stress in correlation with the secretion of apoE and CETP from lipid-loaded macrophages. To this purpose, THP-1 macrophages were loaded with lipids by incubation with human oxidized LDL (oxLDL) and then exposed to human HDL_3. ER stress signaling markers, protein kinase/Jun-amino-terminal kinase (SAPK/JNK p54/p46) and eukaryotic initiation factor-2α (eIF2α), as well as the secreted apoE and CETP, were evaluated by immunoblot analysis. Out of the many different bioactive lipids of oxLDL, we tested the effect of 9-hydroxy-octadecadienoic acid (9-HODE) and 4-hydroxynonenal (4-HNE) on ER stress. Tunicamycin was used as positive control for ER stress induction. Results showed that oxLDL, 9-HODE and 4-HNE induce ER stress in human macrophages by activation of eIF-2α and SAPK/JNK (p54/p46) signaling pathways. OxLDL stimulated apoE and CETP secretion, while tunicamycin determined a reduction of the secreted apoE and CETP, both in control and lipid-loaded macrophages. The addition of HDL_3 to the culture medium of tunicamycin-treated cells induced: (i) the reduction of ER stress, expressed as decreased levels of eIF-2α and SAPK/JNK, and (ii) a partial recovery of the secreted apoE and CETP levels in lipid-loaded macrophages. These data suggest a new mechanism by which HDL_3 diminish ER stress and stimulate cholesterol efflux from lipid-loaded macrophages.

1. Introduction

The focal accumulation of low density lipoproteins (LDL) in the subendothelial space of arteries, where they may undergo oxidative modifications, induce circulating monocytes diapedesis and loading with lipids of monocyte-derived macrophages is the hallmark of atherosclerosis [1]. Oxidized LDL (oxLDL) can induce the unfolded protein response (UPR) and trigger the endoplasmic reticulum (ER) stress in human endothelial cells [2]. ER stress represents a cellular response to transient or prolonged perturbations in ER function (protein synthesis, calcium regulation and intracellular redox potential) [3]. UPR is an adaptive response that first tends to restore normal ER activity and cellular homeostasis, but switches toward apoptosis when ER stress is prolonged, depending on the nature of the agent and of the stress intensity [4,5]. When ER stress occurs, three ER transmembrane sensors, IRE-1 (inositol requiring 1), activating transcription factor (ATF)-6 and PERK (RNA-dependent protein kinase-like ER kinase) are activated [6].

There is increasing evidence that the ER stress in the vascular intima cells, notably macrophages, plays an important role in the atherosclerotic plaque progression. In macrophages, the trafficking of free cholesterol to the ER membrane and its incorporation into the normally cholesterol-poor ER membrane alters the physicochemical properties of this membrane and leads to ER dysfunction [7]. Therefore, excessive accumulation of cholesterol into macrophages may lead to lipotoxic macrophage cell death via UPR-triggered apoptosis [8]. Uptake of oxLDL by macrophages can trigger similar effects, due to the release of free cholesterol from lysosomes and its trafficking to the ER membrane [2]. Recent studies support the idea that phosphorylation of the α-subunit of eukaryotic translation initiation factor 2 (eIF2α) under oxidative stress conditions and accumulation of unfolded proteins in the ER lumen promotes cell apoptosis [6].

Apolipoprotein E (apoE) was proposed as mediator for cholesterol efflux from macrophages in the presence or absence of extracellular acceptors, such as HDL_3 or lipid-free apoA-I [9]. In addition, it is well known that lipid-free apoA-I is a potent inducer of apoE secretion from lipid-loaded macrophages, in a concentration dependent manner [10–12].

Existing data about the molecular mechanism implicated in HDL-mediated regulation of ER stress are incomplete [13]. It was

* Corresponding author. Address: Lipidomics Department, Institute of Cellular Biology and Pathology "N. Simionescu" of the Romanian Academy, 8, B.P. Hasdeu Street, Bucharest 050568, Romania. Fax: +40 21 319 4519.
E-mail address: anca.sima@icbp.ro (A.V. Sima).

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recently shown that HDL are able to prevent both ER stress and the autophagic response triggered by oxLDL in human endothelial cells [14,15]. Our hypothesis was that HDL may impede ER stress in lipid-loaded macrophages by stimulating the cholesterol efflux. To this purpose, we have evaluated the secretion of two proteins involved in macrophage cholesterol efflux from oxLDL-loaded macrophages, apoE and CETP, in the presence or absence of human HDL_3. Furthermore, we investigated HDL_3-mediated modulation of ER-associated signaling pathways in lipid-loaded macrophages: eIF2α and stress-activated protein kinase/Jun-amino-terminal kinase (SAPK/JNK p54/p46), down-stream signaling messengers of PERK, and respectively, IRE-1 [6]. In addition, we explored the effects of two major bioactive lipid components from oxLDL, 9-hydroxy-octadecadienoic acid (9-HODE) and 4-hydroxynonenal (4-HNE) on ER-stress signaling in human macrophages.

2. Materials and methods

2.1. Reagents

RPMI-1640 medium, human and bovine albumin, *o*-phenylenediamine and phorbol-12-myristate-13-acetate (PMA) were purchased from Sigma–Aldrich, St. Louis, MO, USA. Monoclonal or polyclonal antibodies to human apoE, human CETP, and HRP-conjugated goat secondary antibodies against mouse or rabbit IgG were obtained from Abcam, Cambridge, UK. Monoclonal antibody to human β-actin (C4 clone) was purchased from Santa Cruz Biotechnology, Santa Cruz, CA, USA. Monoclonal or polyclonal antibodies to ER stress markers: phospho-eIF2α (Ser51), phospho-SAPK/JNK p54/p46 (Thr182/Tyr185), total-eIF2α, and total-SAPK/JNK p54/p46 were obtained from Cell Signaling, Beverly, MA, USA. (±) 9-hydroxy-10E, 12Z-octadecadienoic acid cholesteryl ester (9-HODE-CE) and 4-hydroxy-nonenal (4-HNE) were obtained from Cayman Chemicals, Ann Arbor, MI, USA.

2.2. Isolation and modification of human lipoproteins

Human LDL and HDL_3 were isolated from plasma of healthy donors from the Blood Transfusion Center Bucharest, by using sequential flotation ultracentrifugation in Optima LE-80 and XP-80 ultracentrifuges (Beckman Coulter International SA, Nyon, Switzerland). Copper-oxidized LDL (oxLDL) was prepared and characterized using the methods previously published [16].

2.3. Cell culture and experimental design

Human THP-1 monocytes were cultured in RPMI-1640 medium containing 10% heat-inactivated fetal calf serum (EuroClone, Siziano, Italy), supplemented with penicillin/streptomycin; monocytes were differentiated into macrophages with 100 nM PMA and seeded onto 6-well plates in growth medium at a density of 10^6 -cells/ml for 72 h prior to the experiment. The activated macrophages were loaded with lipids by 24 h incubation with oxLDL at 100 μg protein/ml in RPMI-1640 supplemented with penicillin/streptomycin. Control cells were exposed in similar conditions to an equivalent amount of human albumin. For specific ER stress signaling pathways investigation, non-loaded and oxLDL-loaded macrophages were exposed to an UPR activator tunicamycin (1 μg/ml) that inhibits protein glycosylation [17].

Macrophages were incubated with human oxLDL or human albumin (100 μg protein/ml) with/without 1 μg/ml tunicamycin for 24 h, the medium was discarded and 20 μg/ml HDL_3 added to the fresh medium for another 24 h. We evaluated apoE and CETP secretion in the culture media, as well as the ER stress associated signaling pathways (eIF2α, SAPK/JNK p54/p46). Alternatively, THP-1 macrophages were exposed for 24 h to 9-HODE-CE (1 and 3 μg/ml) or 4-HNE (10 and 20 μM), and then the ER-stress markers were evaluated.

2.4. Immunoblotting (Western blot) analysis

Culture media collected from macrophages were concentrated 10-fold with an Amicon Ultracel-10 device with a 10 kDa-cutoff (Milipore, Billerica, MA, USA) and were used to quantify the secretion of CETP (by immunobloting analysis) and apoE (by Elisa). Equal amounts of protein from the cell lysates (harvested in RIPA buffer) were subjected to immunobloting analysis. Following the incubation with primary and HRP-conjugated antibodies, a chemiluminescent substrate (Pierce, Rockford, IL, USA) and an ImageQuant LAS4000 imaging system (GE Healthcare Biosciences, Pittsburgh, PA, USA) were used to visualize proteins. The relative protein expression (normalized to β-actin) was determined by densitometry analysis using TotalLab 100 software (Nonlinear Dynamics, Newcastle-upon-Tyne, UK) or ImageQuant-TL software (GE Healthcare Biosciences, Pittsburgh, PA, USA).

2.5. Measurement of apoE in macrophages culture media

Secreted apoE in the macrophage media was measured by Elisa technique, using a development kit according to the manufacturer's instructions (Mabtech, Nacka Strand, Sweden). The *o*-phenylene-diamine reaction was read at 492 nm by using a multiparametric multiwall plate reader M200 Infinity (Tecan Group Ltd., Männedorf, Switzerland). The obtained values were calibrated against a standard curve of recombinant apoE3 (0–10 ng/ml) and normalized to the cellular protein.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 21.0 for Windows (IBM Corporation, Somers, NY, USA). Statistical evaluation was done by independent two-tailed *T*-test and a p value less than 0.05 was considered statistically significant. Data were expressed as mean ± standard deviation (SD).

3. Results

3.1. Oxidized LDL induce ER stress in human macrophages

We have evaluated the ER stress by measuring the activation of ER stress specific markers in THP-1 macrophages loaded with lipids by exposure to oxLDL (100 μg protein/ml) for 24 h. We observed that the activation of the SAPK/JNK (p54/p46) signaling pathway was induced by oxLDL and expressed as increase of the phosphorylation level of p54 (fivefold, $p = 0.0046$) and of p46 (twofold, $p = 0.031$), relative to total p54/p46 and compared to control cells (Fig. 1). Regarding the eIF2α signaling pathway, a lesser activation expressed as 75% ($p = 0.036$) increase of the phospho-eIF2α relative to total-eIF2α in oxLDL-exposed cells compared to control cells was observed (Fig. 1).

We then followed the effect of two of the many different bioactive lipids from oxLDL on ER stress. Therefore, we incubated macrophages either with 9-HODE-CE (1 or 3 μg/ml) or with 4-HNE (10 or 20 μM) added in the culture medium supplemented with human albumin (100 μg/ml). We observed that both 9-HODE-CE and 4-HNE induced the activation of SAPK/JNK signaling pathway. Accordingly, the phosphorylation levels of SAPK/JNK p54 subunit increased sevenfold (1 μg/ml) or 9.5-fold (3 μg/ml), respectively, and that of subunit p46, fourfold, compared to control macrophages. Addition of 4-HNE in the culture medium supplemented

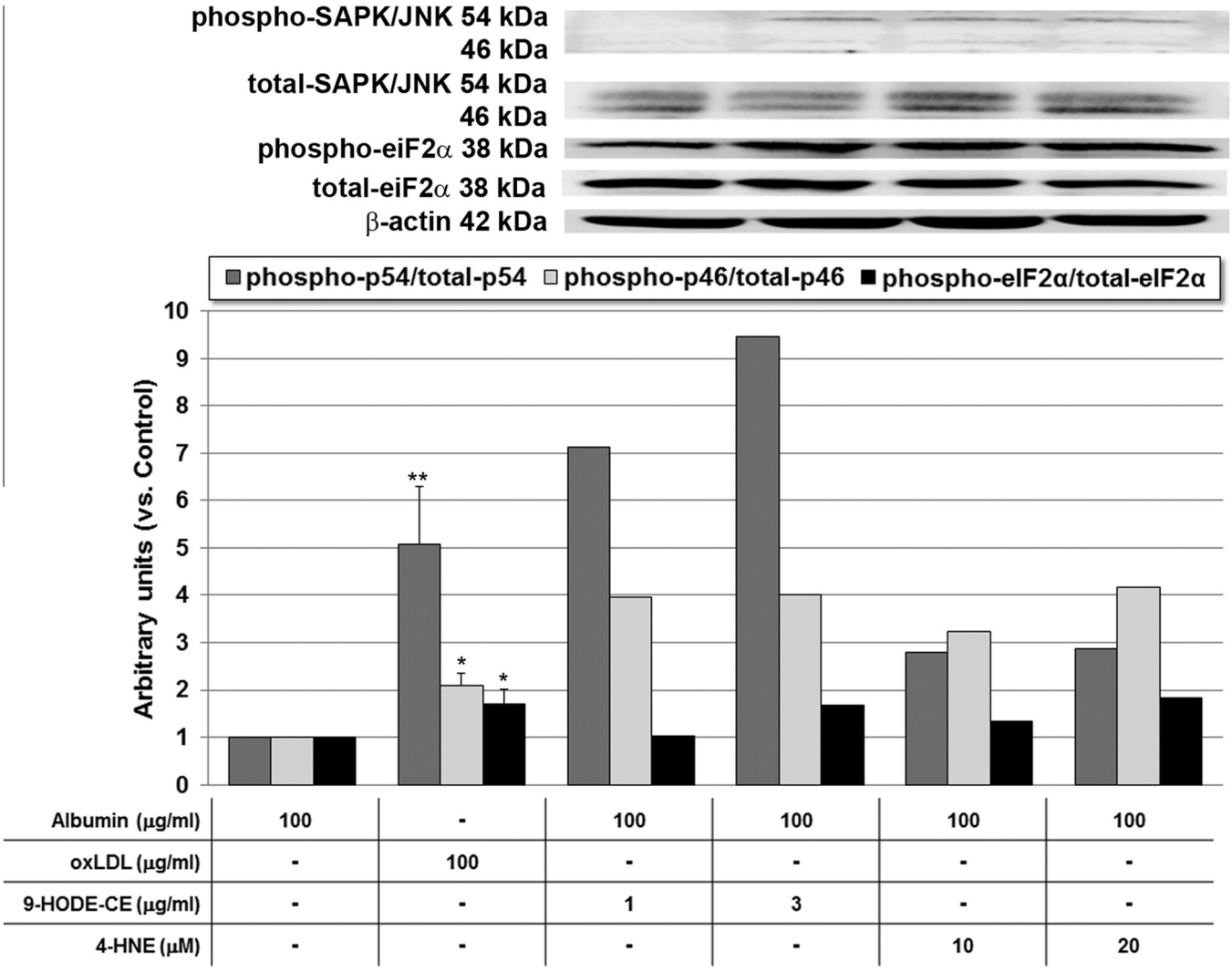

Fig. 1. Modulation of eIF2α and SAPK/JNK signaling pathway in THP-1 macrophages exposed to oxLDL or its major oxidized lipid components, 9-HODE-CE and 4-HNE. Human THP-1 macrophages were loaded with oxLDL (100 μg protein/ml) for 24 h. Alternatively, THP-1 macrophages were exposed to 9-HODE-CE (1 and 3 μg/ml) or 4-HNE (10 and 20 μM). Activation levels of eIF2α signaling was expressed as phospho-eIF2α (Ser51) to total-eIF2α ratio, while of SAPK/JNK signaling as phospho-p54/p46 (Thr183/Tyr185) to total-p54/p46 ratio, both being quantified by immunobloting (WB) in macrophages lysates. $^{*}p < 0.05$, $^{**}p<0.01$ vs. control cells (100 μg human albumin/ml).

with human albumin (100 μg/ml) activated SAPK/JNK p54 subunit threefold (for both 10 and 20 μM 4-HNE) and p46 subunit threefold (10 μM) and fourfold (20 μM), respectively (Fig. 1). The phosphorylation level of eIF2α was increased by 70% only by the higher concentration of 9-HODE-CE (3 μg/ml), while 4-HNE induced a concentration-dependent increase of eIF2α, 35% for 10 μM and 85% for 20 μM (Fig. 1).

3.2. Oxidized LDL amplifies tunicamycin-induced ER stress

We have incubated control and oxLDL-loaded macrophages with tunicamycin (1 μg/ml). As expected, tunicamycin activated the specific ER stress markers of unloaded macrophages, increasing the phosphorylation levels of SAPK/JNK (fourfold the p54 subunit, $p = 0.0017$ and twofold the p46 subunit, $p = 0.037$) and eIF-2α (twofold, $p = 0.003$), as compared to control cells (Fig. 2).

Moreover, the ER stress was amplified by tunicamycin in oxLDL-loaded macrophages, as indicated by the increase of the phosphorylation levels of SAPK/JNK p54 and p46 subunits (fourfold for p54, $p = 0.006$ and twofold for p46, $p = 0.043$) and eIF-2α (1.5-fold, $p = 0.021$) compared to non-loaded cells treated with tunicamycin (Fig. 2). Also, when compared to oxLDL-loaded cells, the ER stress was enhanced by the tunicamycin treatment, as indicated by the increase in SAPK/JNK p54/p46 phosphorylation (by 3.5-fold for p54, $p = 0.012$ and, respectively, by 1.4-fold for p46, $p = 0.027$) and eIF-2α (by 1.8-fold, $p = 0.032$) (Fig. 2).

3.3. HDL_3 reduce ER stress in tunicamycin-treated macrophages

We assessed the role of HDL_3 in the regulation of ER stress and cholesterol efflux from oxLDL-loaded THP-1 macrophages. To this purpose, we incubated THP-1 macrophages with human oxLDL or human albumin (100 μg protein/ml) with/without 1 μg/ml tunicamycin for 24 h, discarded the medium and then added 20 μg/ml HDL_3 to the fresh medium for another 24 h. We used 20 μg/ml HDL_3 because at this concentration we have previously obtained the maximum effect of apoE secretion from lipid-loaded macrophages [11]. We evaluated the reduction of specific ER stress markers by HDL_3 in tunicamycin-treated macrophages. We observed that HDL_3 reduced the activation levels of SAPK/JNK p54 and p46 subunits (1.7-fold for p54, $p = 0.0019$ and 1.3-fold for p46,

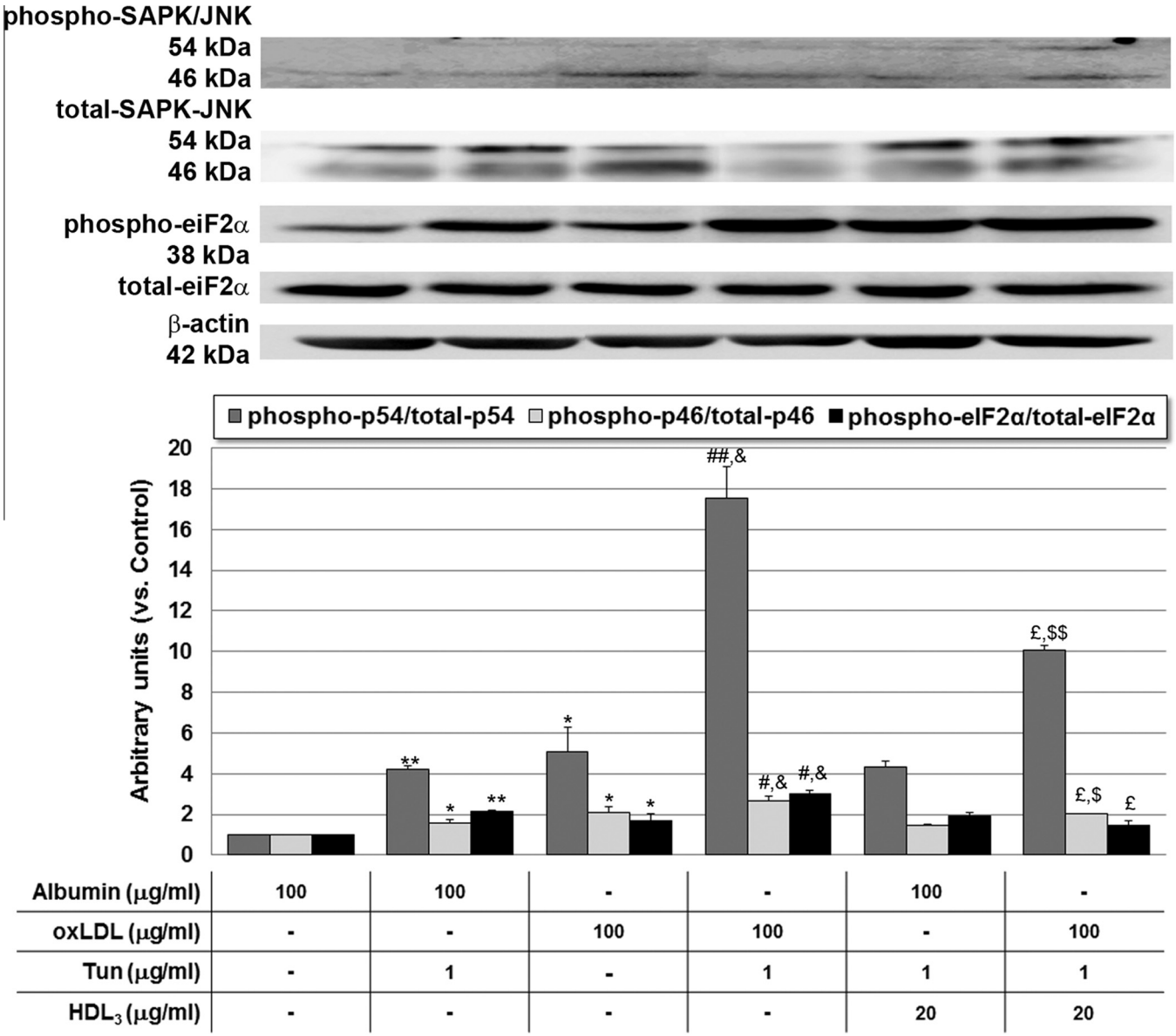

Fig. 2. Modulation of SAPK/JNK and eIF2α signaling pathways in lipid-loaded macrophages subjected to ER stress. Human THP-1 macrophages were loaded with oxLDL (100 μg protein/ml) and exposed to tunicamycin (Tun)-induced ER-stress (1 μg/ml) in the presence/absence of 20 μg/ml HDL_3. Activation levels of SAPK/JNK and eIF2α, expressed as phospho-p54/p46 (Thr183/Tyr185) to total-p54/p46, and respectively phospho-eIF2α (Ser51) to total-eIF2α ratio were quantified by immunobloting (WB) in macrophages lysates. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. control cells (100 μg human albumin/ml); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. Tun; $^{\&}p < 0.05$ vs. oxLDL; $^{£}p < 0.05$ vs. oxLDL + Tun, $^{\$}p < 0.05$, $^{\$\$}p < 0.01$ vs. HDL_3 + Tun.

$p = 0.035$) and eIF-2α (twofold, $p = 0.015$), but only in lipid-loaded macrophages (Fig. 2).

3.4. HDL_3 increase apoE and CETP secretion from control and lipid-loaded macrophages

We have assessed the secretion of apoE and CETP from control and lipid-loaded macrophages. As previously reported, an increase of 70% for apoE ($p < 0.001$) and 45% for CETP ($p = 0.017$) secretion from lipid-loaded macrophages compared to control cells (THP-1 macrophages incubated with 100 μg/ml human albumin, 24 h) was measured (Fig. 3). The addition of tunicamycin significantly reduced the secretion of apoE (by 50%, $p < 0.001$) and CETP (by 40%, $p = 0.039$) in control macrophages, as well as in oxLDL-loaded macrophages (45%, $p = 0.003$ for apoE, and 65%, $p = 0.0028$ for CETP) (Fig. 3).

The addition of HDL_3 significantly increased apoE (2.8-fold, $p < 0.001$) and CETP (1.2-fold, $p = 0.032$) secretion from non-loaded cells incubated with tunicamycin (Fig. 3). HDL_3 addition to oxLDL-loaded macrophages treated with tunicamycin increased apoE (2.4-fold, $p < 0.001$) and CETP (twofold, $p = 0.024$) secretion, compared to oxLDL-loaded cells treated with tunicamycin (Fig. 3). Interestingly, the size of HDL_3 particles at the end of the incubation with oxLDL-loaded macrophages increased from 5.5 to 9.6 nm, as measured by using a Nicomp-380 submicron analyzer (Agilent, Santa Clara, CA, USA).

4. Discussions

Data from the present study show that ER stress is induced in human macrophages by exposure to oxidized LDL (in good agreement with Sanson et al. and Devries-Seimon et al. [2,8]) and in particular by the two major oxidation-generated lipid components of

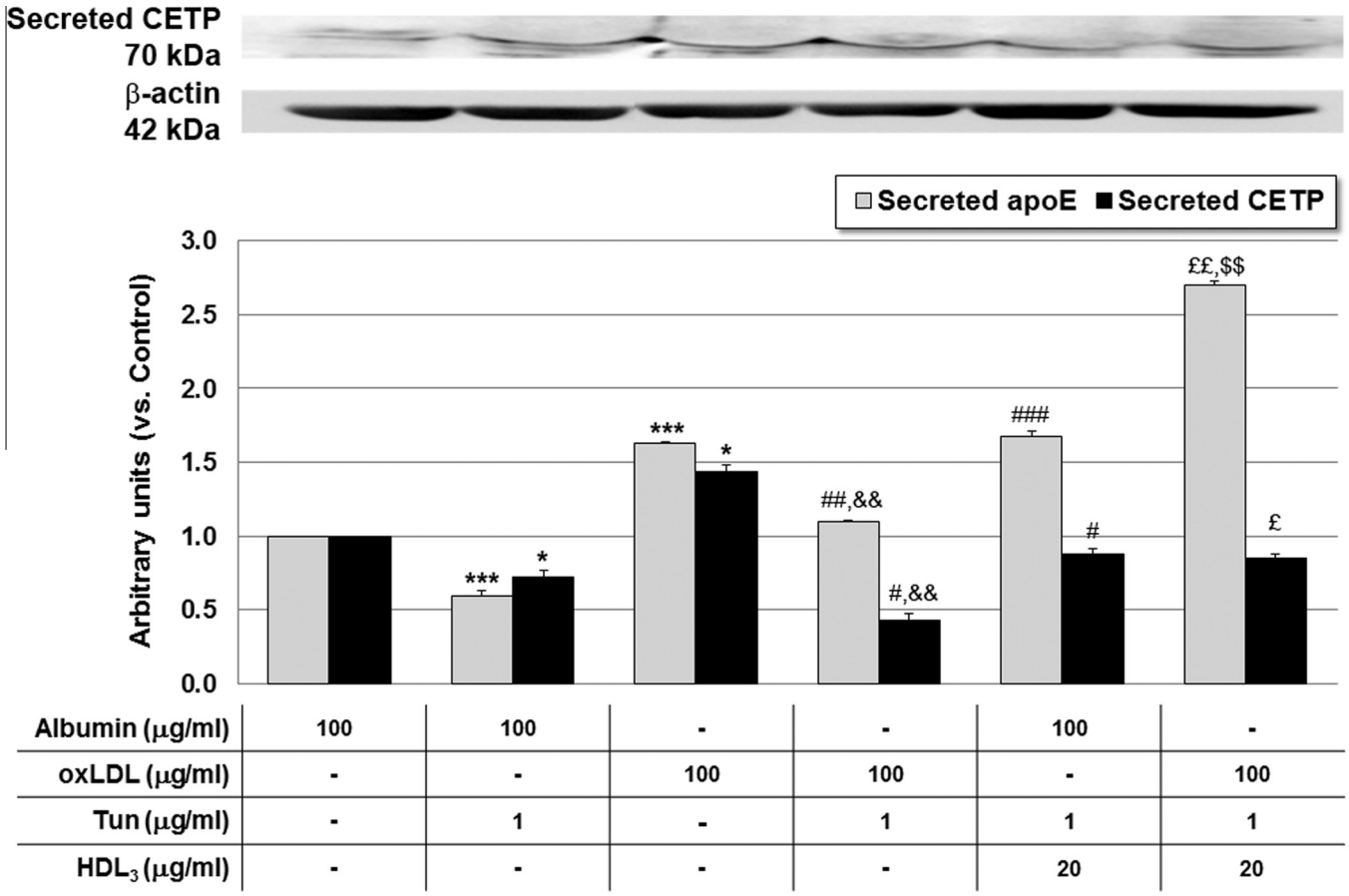

Fig. 3. Secreted apoE and CETP levels in culture media from THP-1 macrophages subjected to ER stress. Human THP-1 macrophages were loaded with oxLDL (100 μg protein/ml) and then exposed to tunicamycin (Tun)-induced ER-stress (1 μg/ml) in the presence/absence of 20 μg/ml HDL_3. Secretion of apoE was quantified in macrophages' media by Elisa technique (expressed as ng apoE/mg cell protein), while secreted CETP was assessed by immunoblotting (after concentration with 10 kDa cut-off filters). $^{*}p < 0.05$, $^{***}p < 0.001$ vs. control cells (100 μg human albumin/ml); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. Tun; $^{\&\&}p < 0.01$ vs. oxLDL; $^{£}p < 0.05$, $^{££}p < 0.01$ vs. oxLDL + Tun; $^{\$\$}p < 0.01$ vs. HDL_3 + Tun.

oxLDL, 9-HODE and 4-HNE, which activate SAPK/JNK and eIF2α signaling pathway. We also report here that HDL_3 down-regulate ER-stress by stimulating apoE and CETP secretion from lipid-loaded macrophages, a process correlated with cholesterol efflux [18,19].

The known stressors that can lead to prolonged activation of UPR and ER stress include oxidative stress, oxysterols and high levels of intracellular free cholesterol and/or saturated fatty acids [6]. Existing data suggest that cholesterol accumulation in macrophages activates UPR and C/EBP homologous protein (CHOP)-induced apoptosis and the inflammatory pathways [8,20,21]. In the present study we demonstrate that two major bioactive lipid components from oxLDL, 9-HODE and 4-HNE, induce ER stress in human macrophages. Therefore, we suggest the addition of 9-HODE to the list of molecules that may induce ER stress, along with 4-HNE, as was recently reported [22].

Published data show that apoE is secreted by macrophages and macrophage-derived foam cells [23] and that macrophage-derived apoE, but not systemic apoE, is employed for the reverse cholesterol transport (RCT) from macrophages [19]. Macrophages from the arterial wall secrete CETP that can also contribute to RCT as part of the remodeling cascade required for the effective interaction of HDL with the scavenger receptor B-I and the subsequent selective delivery of cholesteryl esters to the liver [23,24]. In the present study, we demonstrate that oxLDL loading increase apoE and CETP secretion (in good agreement with [23,25–27]) and induce ER stress (confirming the results of Muller et al. [15]). This result is in agreement with a recent study showing that although cholesterol accumulation induces a mild increase in ER stress markers in CHO cells and human macrophages, the induction of ER stress may not by itself be sufficient for the inhibition of apoE secretion [28].

Existing data demonstrate that the main protein from HDL_3, apoA-I, stimulates the secretion of apoE from lipid-loaded macrophages, mainly by a molecular mechanism related to the activation of protein kinase A (PKA) and by the inhibition of nuclear factor (NF)-κB signaling pathway [12,29]. We demonstrate in the present study that HDL_3 can down-regulate the ER-stress by increasing the secretion of apoE from macrophages incubated with tunicamycin and therefore inducing the apoE-dependent cholesterol efflux [18,19]. This result is in agreement with the study of Kockx et al. [28] who suggest that in CHO cells, despite the presence of ER stress, the removal of excess cholesterol can be restored by the apoE secretion. They conclude that strategies to normalize cellular cholesterol content *in vivo* may restore the normal homoeostatic processes and intracellular protein transport. However, in our study this effect was observed only in lipid-loaded macrophages, HDL_3 being unable to modulate the tunicamycin-induced ER stress in non-loaded macrophages. This latter result might strengthen our hypothesis that HDL_3 reduces ER stress by stimulating cholesterol efflux, in agreement with Muller et al. who reported that HDL can prevent the oxLDL-induced activation of the ER stress sensors

in human endothelial cells and subsequent activation of the pro-apoptotic signals [15].

In conclusion, our results suggest a new mechanism by which HDL may protect the intimal macrophages from oxLDL-induced ER stress by inhibiting eIF2α and SAPK/JNK signaling pathways through stimulation of apoE and CETP secretion and, subsequently, cholesterol efflux. Targeted inhibition of ER stress signaling by the stimulation of HDL trafficking pathways could provide unique opportunities to stop or reverse the atherosclerotic process.

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