Int J Clin Exp Med 2016;9(6):10529-10536
www.ijcem.com /ISSN:1940-5901/IJCEM0022416

*Original Article*

# KDELC1, a novel endoplasmic reticulum resident glycoprotein in hepatic dysfunction

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Received December 21, 2015; Accepted April 3, 2016; Epub June 15, 2016; Published June 30, 2016

**Abstract:** Several endoplasmic reticulum resident proteins contain a unique C-terminal sequence Lys-Asp-Glu-Leu KDEL which is required for the retention of these proteins in the endoplasmic reticulum. To reveal the expression and possible role of KDELC1 in hepatic dysfunction, we used enzyme-linked immunosorbent assay (ELISA) to study the expression of KDELC1 in sera of hepatic dysfunction patients. Our findings suggest that KDELC1 is up expression in sera of hepatic dysfunction patients. By immunohistochemical staining, western blot and flow cytometer assay, we further show that KDELC1 localizes to the lumen of the endoplasmic reticulum, participates in the response of endoplasmic reticulum stress and regulates the HepG2 cell proliferation. These interesting observations suggested that KDELC1 might have important roles in both physiological and pathological processes in hepatic dysfunction.

**Keywords:** KDELC1, glycoprotein, endoplasmic reticulum stress, cell proliferation, hepatic dysfunction

## Introduction

The endoplasmic reticulum (ER) is the cellular organelle for the synthesis, assembly, and glycosylation of proteins that are destined for secretion or transport to the cell surface [1, 2]. To mediate these functions, the ER contains a number of soluble resident proteins which act as molecular chaperones assisting in protein folding and assembly [3, 4]. Many of these ER resident proteins contain special amino acid sequences that cause their specific retention in the ER [5]. The sequence Lys-Asp-Glu-Leu KDEL or a closely related sequence is present at the extreme carboxyl terminus of several soluble ER resident proteins [6]. It is commonly accepted that proteins carrying this motif are bound by a KDEL receptor in the Golgi apparatus and that the receptor-ligand complex returns to the ER [7]. These KDEL proteins are chaperones which associate with other proteins during the processes of folding and maturation.

A novel KDEL motif-bearing protein, KDELC1 (also known as EP58 and MGC5302), has been identified recently [8]. KDELC1 is a small gene with 10 exons spanning ~15 kb and encodes a protein product localized to the lumen of the endoplasmic reticulum. The KDELC1 protein bears no significant sequence similarity to other known ER proteins. It contains a conserved functional domain which suggests an involvement in polysaccharide biosynthesis [9, 10]. Unfortunately, less information is available about the functional characters of KDELC1.

Furthermore, the KDELC1 belongs to a large family of secreted and transmembrane proteins that have key roles in important biological processes such as morphogenesis, cellular differentiation, apoptosis, and modulation of the immune response, as well as disease processes such as cancer progression [11, 12]. Previous studies indicated that KDELC1 exhibited elevated expression in TGF-β1 activated human hepatic stellate cells LX-2 treated with rhDecorin [13]. In summary, the available data demonstrated that KDELC1 might have important roles in proliferation, inflammation and signaling in cells.

Hepatocytes are rich in ER like other secretory cells. Because of their high protein synthesizing

capacity, it is easy to suppose that ER stress response play an important role in various liver diseases. ER stress response accompanies nearly all forms of acute and chronic liver injury. In order to identify novel functions of ER resident protein KDELC1 in liver injury of human, we expressed and purified KDELC1 protein for preparation the polyclonal antibody previously. In the present study, we detected the spatial expression patterns of KDELC1 in sera of hepatic dysfunction patients at the protein level and investigated the role of KDELC1 in the endoplasmic reticulum especially ER stress. Moreover, we have analyzed the effect of KDELC1 on the cell cycle by up and down-regulated KDELC1 expression. Here, we report that KDELC1 might have relationship with the hepatic dysfunction, participates in the response of ER stress and regulates the HepG2 cell proliferation.

## Material and methods

### *ELISA*

To explore the role of KDELC1 in regulating hepatic pathological processes, the indirect competitive ELISA format was adopted for analyzing the KDELC1 expression in sera of hepatic dysfunction patients. A total of 183 hepatic dysfunction and normal persons were collected for inclusion at the BeiJing DiTan Hospital in accordance with the local ethical regulation. Hepatic dysfunction groups were considered eligible if they ALT level above 40 U/L at 37°C.

The ELISA procedures were as follows. Microtiter plates were coated with 50 μL/well sera as antigen in sodium carbonate buffer, pH 9.6, and were incubated overnight at 4°C. After washing twice 200 μL/well of phosphate-buffered saline, pH7.5, containing 0.05% (v/v) Tween 20, and plates were left for 2 h at 37°C with 200 μL/well of 5% BSA/PBST, to reduce non-specific binding, and were washed twice as above. And then the plates were incubated with purified rabbit anti-KDELC1 in a final volume of 100 μL (1:50 dilution) for 2 h at 37°C. After five times washes with PBS, the plates were incubated with goat anti-rabbit IgG conjugated to HRP (1:1000 dilution) at 37°C for 2 hours. Washing plates again, 100 μL of TMB was added to each well and stored in the dark for 5 min. Sulfuric acid (5%, 50 μL/well) was added to stop the enzyme reaction and the absorbance was measured at 450 nm with ELISA reader.

### *Plasmids*

To determine its subcellular distribution, the coding region of human KDELC1 was cloned into pEGFP-C1 vector using *Hind* III and *Kpn* I (Takara, China) to create pEGFP-C1-KDELC1, which produced recombinant KDELC1 and EGFP from the same plasmid. The pERFP-calreticulin plasmid (kindly supplied by Prof. Wei) was used as the specific ER marker in this study. HepG2 cells at 60-70% confluence were co-transfected with above plasmids by using Lipofectamine™ 2000 transfection reagent according to the manufacturer's instruction (Invitrogen, USA). Cells were observed under a laser scanning confocal microscope (Zeiss LSM510 META, Germany).

### *Cell culture and treatment*

Human hepatoblastoma HepG2 cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM, Gibco, USA) supplemented with 10% FBS (Gibco, USA), 100 U/ml penicillin and 100 μg/ml streptomycin at 37°C in humified air with 5% $CO_2$. Cells at approximately 80% confluence were washed twice in PBS and incubated with serum-free DMEM containing 2 and 4 μg/ml tunicamycin for 24 h and 48 h before cell harvest for analyses respectively. Tunicamycin is the ER stress agent, which inhibits protein glycosylation in the ER [14].

### *RNA interference (RNAi)*

To knockdown the expression of KDELC1 protein, RNAi was performed as described with the use of pcDNA6.2-GW/EmGFPmir-KDELC1 shRNA plasmids (Invitrogen, USA). RNAi experiments followed the manufacturer's protocol. KDELC1 shRNA plasmids were transfected into HepG2 cells by use of Lipofectamine™ 2000 (Invitrogen, USA). We examined the expression of KDELC1 at 48 h after transfection using Western blotting assay. Furthermore, to evaluate shRNA-mediated gene silence, scramble shRNA was used as control.

### *Western blot analysis*

Western blot analysis was performed as described [17]. After being treated as mentioned

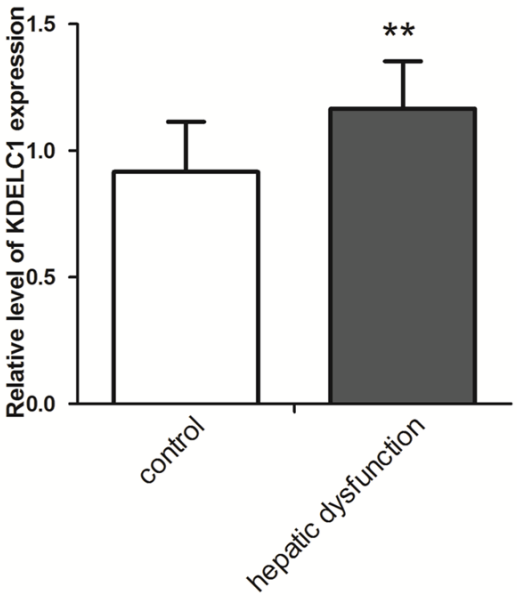


**Figure 1.** Effect of KDELC1 on the hepatic dysfunction. The expressions of KDELC1 in hepatic injury serum were anglicized by ELISA method. ELISA data demonstrate that KDELC1 was down-regulated in hepatic dysfunction group (n=87) compared with the control group (n=96), $P<0.01$.

above, cells were lysed in lysis buffer containing 25 mM Tris-HCl (pH 6.8), 2% SDS, 6% glycerol, 1% 2-mercaptoethanol, 2 mM PMSF, 0.2‰ bromphenol blue and a protease inhibitor cocktail (Sigma, USA) for 10 min at room temperature and boiled for another 10 min. Equal amounts of total proteins (40 μg) underwent SDS-PAGE and were electroblotted onto PVDF membrane (Millipore, USA). The membrane was blocked with 5% (w/v) nonfat dry milk in PBS-Tween 20 (PBST; 0.05%) for 1 h and incubated with primary antibody (1:200~1:1000 dilution) at 4°C overnight. After a washing in PBST and PBS, the PVDF membrane was incubated with appropriate horseradish peroxidase-conjugated secondary antibodies (1:5000 dilution) for 1 h at room temperature. The immunoreactive bands were chromogenously developed with 3, 3'- diaminobenzidine. β-Actin was used as loading control.

*Cell cycle analysis by flow cytometer*

To elucidate roles of KDELC1 during cell cycle regulation, we performed gain-of-function and loss-of-function experiments using pEGFP-C1-KDELC1 and pcDNA6.2-GW/EmGFP-mir-KDELC1 shRNA plasmids in HepG2 cells. HepG2 cells at 60-70% confluence were transfected with above plasmids respectively by using Lipofectamine™ 2000 (Invitrogen, USA). Furthermore, scrambled shRNA and pEGFP-C1 plasmids were used as controls.

After 48 h of transfection, cells were detached and fixed with 70% ethanol at -20°C for 2 h. Subsequently, the cells were washed with PBS and were re-suspended in 0.5ml of manipulation medium and 0.15 mg of RNAse with 15 μg of propidium iodide added. Cells were incubated at room temperature in darkness for 1 h. Flow cytometer (BD Biosciences, USA) was used to analyze the stage of cell cycle of 5,000 individual cells in each group.

*Statistics analysis*

Data were expressed as mean ± S.E. and accompanied by the number of independent experiments. Statistics analysis was done by Student's t-test, and differences of $P<0.05$ were considered statistically significant.

## Results

*Relationship between KDELC1 and hepatic injury*

KDELC1 which was abundantly expressed in liver indicates its importance in the live function. In order to explore the relationship between KDELC1 and hepatic injury, a total of 183 hepatic dysfunction and normal persons were collected for inclusion at the BeiJing DiTan Hospital. The characters of KDELC1 expression is anglicized by ELISA method. ELISA data demonstrate that KDELC1 was up-regulated in hepatic dysfunction group compared with the control group, $P<0.01$ (**Figure 1**).

*Location characterizations of KDELC1*

To investigate the functional characterization of KDELC1, we first expressed KDELC1 protein and prepared the polyclonal antibody of KDELC1 (data not shown). Then, we detected the location of KDELC1 in HepG2 cell line by using pEGFP-KDELC1/pERFP -calreticulin plasmids co-transfection. After co-transfected with pEGFP-KDELC1/pERFP -calreticulin plasmids into HepG2 cell for 48 h, the images of Laser scanning confocal microscope indicated that KDELC1 located in endoplasmic reticulum (**Figure 2**).

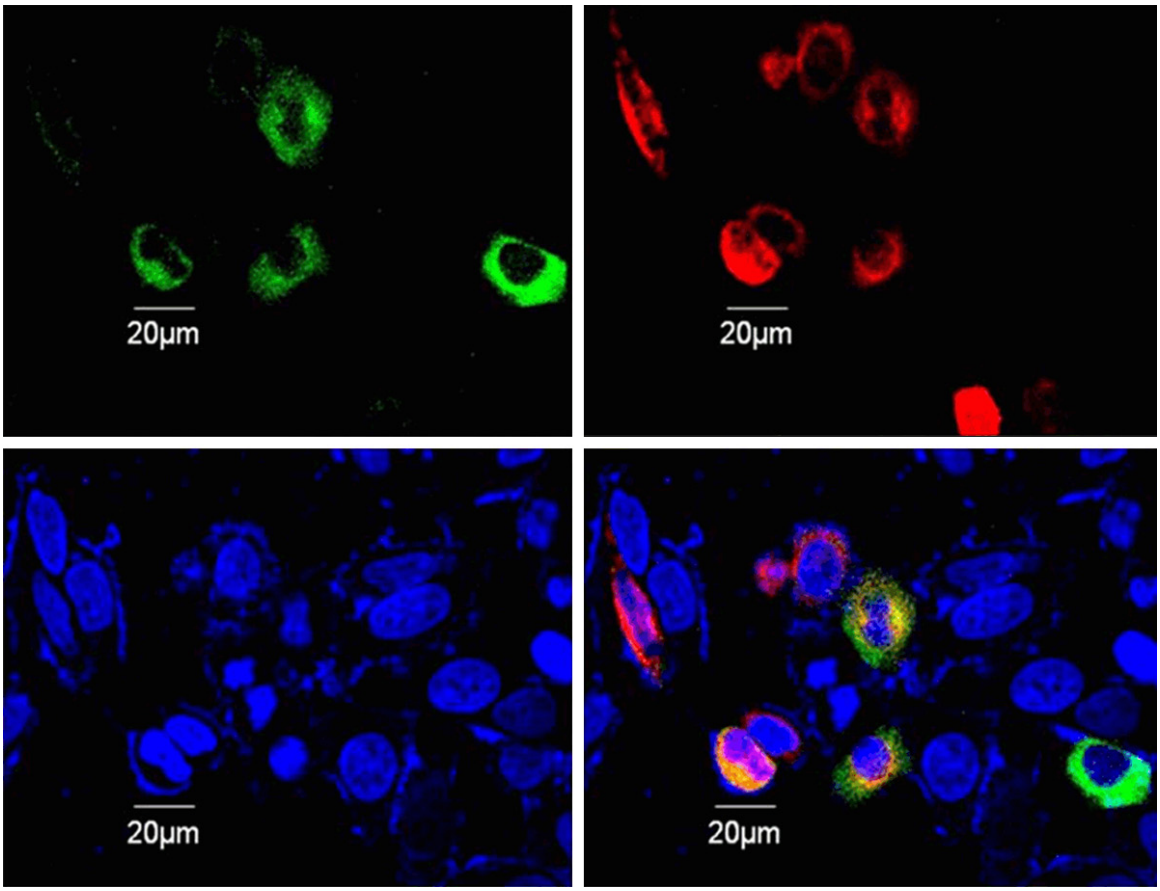


**Figure 2.** Subcellular location of KDELC1 in HepG2 cell line. HepG2 cell were co-transfected using pEGFP-KDELC1/pERFP -calreticulin plasmids. Confocal laser-scanning micrographs of the cells are shown for staining of KDELC1 (green) and calreticulin (red), PI staining indicates the cell nuclei (blue). The merged cells indicated that KDELC1 located in endoplasmic reticulum.

*Effect of KDELC1 on endoplasmic reticulum stress in HepG2 cell*

It is well known that expression of several ER-resident proteins is stimulated at the transcriptional level by ER stress [18]. Induction of GRP78 gene expression has been used extensively as a marker for the ER stress [19]. We tested whether KDELC1 gene expression could be increased by ER stress in current study. The HepG2 cells were treated with ER stress agent tunicamycin, which inhibits protein glycosylation in the ER. Western blot results showed that 4 μg/ml tunicamycin increased KDELC1 protein expression level parallel with GRP78, while having no effect on β-actin protein content (**Figure 3**).

*Regulation of KDELC1 protein expression in HepG2 cells*

To explore the function of KDELC1 in HepG2 cells, up or down-regulated its expression by use of the pEGFP-C1-KDELC1 or pcDNA6.2-GW/EmGFPmir-KDELC1 shRNA plasmids were performed in the present study. Confocal microscopy of HepG2 cells transfected with non-silencing GFP-labeled shRNA plasmid revealed a transfection efficiency of plasmids above 90% (**Figure 4A**).

Western blot result showed that scrambled shRNA and pEGFP-C1 control plasmids have no effect on level of KDELC1 (**Figure 4B**), but transfected with pEGFP-C1-KDELC1 up-regulated the level of KDELC1 obviously and pcDNA6.2-GW/EmGFPmir-KDELC1 shRNA mediated knockdown of KDELC1 expression significantly (**Figure 4B**).

*Effect of KDELC1 on the cell cycle of HepG2 cells*

Cell cycle was evaluated by flow cytometer assay after up and down-regulation of KDELC1.

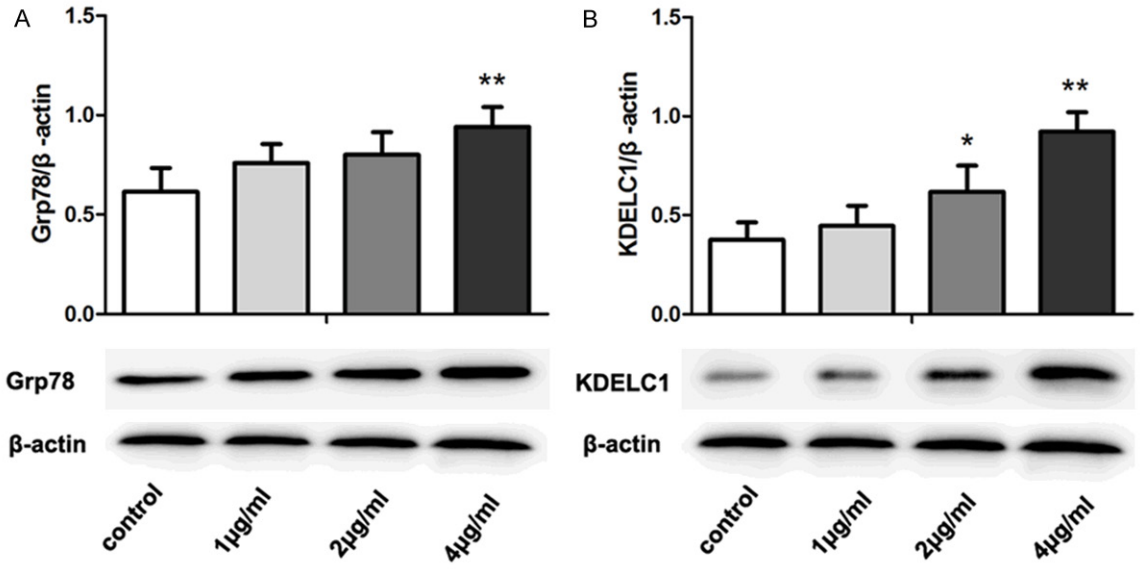


**Figure 3.** Effect of KDELC1 on ER stress in HepG2 cells. Western blot analysis of proteins after treatment with 2 μg/ml, 4 μg/ml tunicamycin for 24 h. Tunicamycin increased KDELC1 protein expression level parallel with GRP78, while having no effect on β-actin protein content.

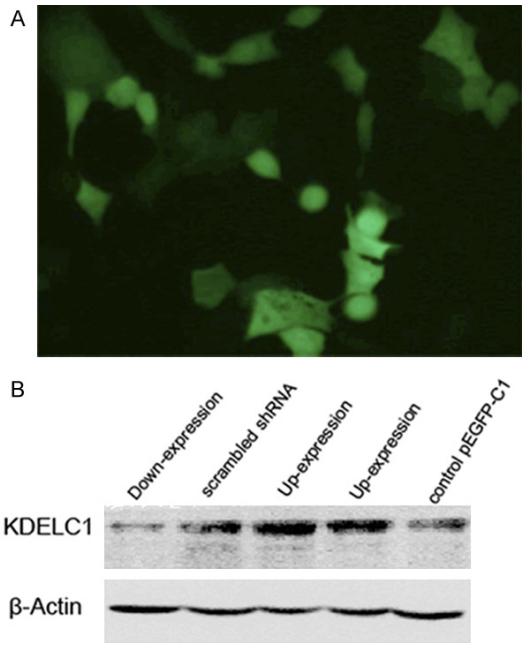


**Figure 4.** Regulation of KDELC1 protein expression in HepG2 cells. A. Fluorescent micrographs of HepG2 cells transfected with non-silencing GFP-labeled scrambled shRNA for 24 h. B. Western blot analysis of KDELC1 up- or down-regulation mediated by its pEGFP-C1-KDELC1 or pcDNA6.2-GW/EmGFPmir-KDELC1 shRNA plasmids in HepG2 cells. Protein extracts were from the cells transfected with plasmids for 48 h.

As shown in **Figure 5**, overexpression of KDELC1 in HepG2 cell induced cell cycle arrest as exemplified by the increased number of cells in the S-phase. Flow cytometer results showed that up-regulated KDELC1 could inhibit cell proliferation. However, down-regulated KDELC1 could induce cell proliferation. This result indicates that KDELC1 is able to inhibit proliferation of HepG2 cell and induce its apoptosis.

## Discussion

Several ER resident proteins contain a unique C-terminal sequence (KDEL) which is required for the retention of these proteins in the ER. The ER resident proteins act as molecular chaperones assisting in protein folding and assembly [20]. KDELC1 is a novel KDEL motif-bearing ER resident glycoprotein. However, its functions are not well understood. For understanding the function of KDELC1, we firstly expressed and purified KDELC1 protein, prepared the polyclonal antibody of KDELC1. In this study, the subcellular localization of KDELC1 in the ER was confirmed by pEGFP-KDELC1/pERFP-Calreticulin plasmids co-transfection. The ER resident protein Calreticulin (Crt), a $Ca^{2+}$ binding chaperone, is a molecular chaperone that associates transiently with many newly synthesized proteins, especially with glycoproteins via its lectin domain [21]. The ER distribution of KDELC1 suggests that it might play a pivotal role in regulating the protein folding.

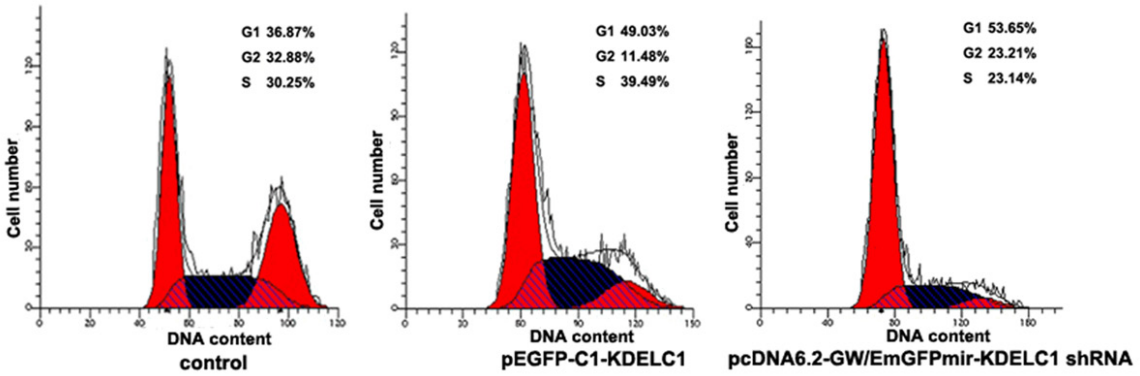


**Figure 5.** Effect of KDELC1 on the cell cycle. KDELC1 overexpression in HepG2 cell delayed cell cycle expression and induced apoptosis of HepG2. Low expression of KDELC1 in HepG2 cell accelerated cell cycle expression.

It is commonly accepted that KDEL proteins are bound by a receptor located in the Golgi apparatus so that the receptor-ligand complex returns to ER [22, 23]. The KDEL receptor represents an important class of proteins that is necessary for the recovery of ER resident chaperones from the late secretory compartments back to the ER. This role can be envisaged as part of a wider function in the coordination of ER quality control and the unfolded protein response (UPR) [24]. It also has been reported that the KDEL receptor is associated with stress-dependent activation of p38 mitogen-activated protein kinases and c-Jun amino-terminal kinases (JNKs) [25]. Since MAPK signalling has been implicated in a variety of processes, such as cell development, differentiation, survival and death, it is conceivable that KDELC1-receptor complex might have important roles in both physiological and pathological processes.

Recent studies define ER as an important integrator of physiological or pathological, external and internal stimuli [26]. Imbalance between demand and capacity leads to ER stress response, which is characterized by over-expression of ER chaperones, inhibition of protein synthesis, and degradation of misfolded proteins [27, 28]. It is well known that expression of several ER resident proteins is stimulated by ER stress. The impressive up-regulation of ER resident glucoseregulated protein 78 (GRP78) exemplifies its important role in maintaining ER homeostasis and in the control of the UPR. Accordingly, GRP78 gene expression has been used extensively as a marker for the ER stress [29].

However, the previous study indicated that unlike various other ER-resident chaperones, EP58 (homology of KDELC1 in mouse) was poorly induced at the transcription level by ER stress as tested in macrophage cell line WEHI-3 [8]. So in current study, we ascertained whether ER stress increases KDELC1 gene expression in human HepG2 cells. It is worth noting that ER stress inducers tunicamycin increased KDELC1 gene expression and protein content several-fold in parallel with GRP78 in HepG2 cells, suggesting that the function of KDELC1 was related to the response of ER stress.

Furthermore, we both described the roles of KDELC1 in the human hepatoblastoma HepG2 cell (in vitro) and explored the expression of KDELC1 in sera of hepatic dysfunction patients (in vivo). Study in vitro has shown that knockdown of KDELC1 by its specific shRNA induced the cell proliferation,which suggests the essential role in regulating HepG2 cell physiological processes.

Several diseases, such as familial hypercholesterolemia (FH) and cystic fibrosis (CF), are caused by defects in the cellular protein secretion pathway, particularly in the ER [30, 31]. The protein secretion pathway involves several control mechanisms that ensure the correct folding and modification of secreted proteins. The differential transcription of ER resident protein genes has been demonstrated in several diseases and in several model systems for ER stress [32-34]. Since higher expression of KDELC1 was detected in hepatic dysfunction group in our present study, KDELC1 might play

pivotal roles in regulating hepatic pathological processes.

In summary, KDELC1 is localized to the lumen of the endoplasmic reticulum and preponderantly expresses in liver. KDELC1 participates in the response of ER stress, regulates the HepG2 cell proliferation and might have relationship with the hepatic dysfunction. The discovery of the novel ER resident-glycoprotein KDELC1 functions might lead to an understanding of disease paradigms and provide new opportunities for development of drug therapies for treatment of the wide range of diseases for which there is still no cure.

## Acknowledgements

This work was supported financially by the Development Plan of Science and Technology in Shandong Province (Project Nos. 2012G0021855).

## Disclosure of conflict of interest

None.

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