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IDOL, inducible degrader of low-density lipoprotein receptor, serves as a potential therapeutic target for dyslipidemia

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ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) is the hall marker for the atherosclerotic cardiovascular disease (ASCVD). It has been shown that over 70% of circulating LDL-C is metabolized through binding and activation of hepatic LDL receptor (LDLR). Genetic LDLR mutations cause hypercholesterolemia in the patients. Therefore, elevation of LDLR levels is beneficial for the treatment of dyslipidemia. LDLR expression is regulated by the SREBP2/PCSK9 pathways. Targeting SREBP2/PCSK9 pathways by statins and human monoclonal PCSK9 antibody has been shown to reduce the progression of ASVCD. Recent studies identified that inducible degrader of LDLR (IDOL) is a novel regulator of LDLR. IDOL is an E3-ubiquitin ligase regulated via liver X receptors (LXRs) binding to the upstream of translation start site of IDOL. IDOL modulates LDLR distribution through ubiquitination and degradation of LDLR in lysosomes. Genome-wide association studies (GWAS) have revealed that the nonsynonymous substitution rs9370867 of IDOL probably contributes to the variability of circulating LDL levels. Recently studies also demonstrated that IDOL influences PCSK9 expression in a LDLR/SREBP2-dependent manner. Based upon these novel findings, we hypothesize that IDOL and PCSK9 would have a synergistic effect on LDLR distribution. Specifically, loss of IDOL increases LDLR distribution in the hepatic cell, and subsequently reduces serum LDL-C levels in dyslipidemic patients. IDOL might be a potential therapeutic target for the treatment of ASCVD.

Introduction

The primary goal for treatment of patients with dyslipidemia is to reduce non-high-density lipoprotein cholesterol (non-HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels according to the 2014 National Lipid Association (NLA) recommendations for management of dyslipidemia [1]. High levels of non-HDL-C and LDL-C are the hall markers of atherosclerosis as well as atherosclerotic cardiovascular disease (ASCVD). Although they are important, controlling both the non-HDL-C and LDL-C levels in serum is a huge challenge. Statins, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitors, have been widely used for the treatment of dyslipidemia [2]. Unfortunately, the higher dose of statins also increases unwanted side effects, such as myalgia and rhabdomyolysis [3,4]. Therefore, it is urgent to identify the novel metabolic pathways of serum LDL-C and to explore new targets for the treatment of dyslipidemia in humans.

Studies have shown that more than 70% of circulating LDL-C is eliminated via endocytosis by the hepatic LDL receptor (LDLR) [5,6]. Mutations in LDLR also cause familial hypercholesterolemia and increase the risk of ASCVD [5,6]. LDLR is known to be regulated through multiple signaling pathways in response to cellular cholesterol levels [7–9]. Among them, the most important regulator is sterol response element-binding protein 2 (SREBP2). Active

Abbreviations: Non-HDL-C, non-high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SREBPs, sterol response element binding proteins; PCSK9, pro-protein convertase subtilisin/kexin type 9; IDOL, inducible degrader of LDLR; LXRs, liver X receptors; MYLIP, myosin regulatory light chain interacting protein; FERM, frame of ezrin/radixin/moesin homology; RING, really interesting new gene; PTB, phosphotyrosine-binding; MVB, multivesicular body.

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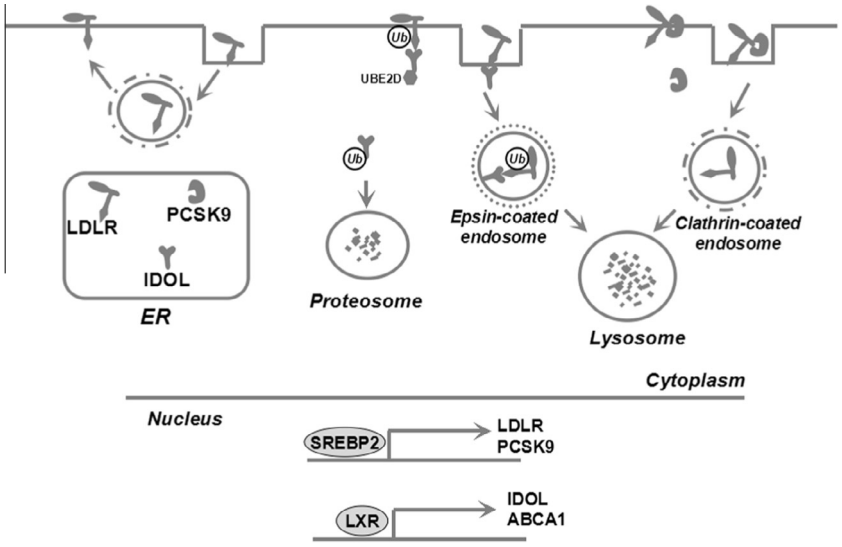

Fig. 1. Hepatic LDLR distribution is modulated by three pathways. The first regulator is the active form of nuclear SREBPs, which regulate LDLR expression by binding to SRE located upstream of the LDLR promoter according to the endoplasmic reticulum cholesterol levels. The second regulator is PCSK9, which binds to the LDLR at the cell surface and reroutes the internalized LDLR to intracellular degradation; this regulator has been associated with an 88% reduction of ASCVD events. The third regulator, IDOL, is recruited to the plasma membrane by LDLR, and subsequently, USP8 and ESCRT complexes are used to facilitate LDLR degradation in the lysosome by the MVB protein-sorting pathway and to catalyze its own degradation in the proteasome.

form of SREBP2 regulates LDLR expression through binding to SRE located in the upstream of the LDLR promoter. The second key regulator of LDLR is PCSK9 (pro-protein convertase subtilisin/kexin type 9), which binds to LDLR at cell surface and redirects the internalized LDLR for intracellular degradation [10]. Inhibition of PCSK9 has been associated with reduction of ASCVD [11–13]. Inhibition of PCSK9 activity using human monoclonal IgG2 antibody against PCSK9, such as evolocumab developed by Amgen and alirocumab developed by Regeneron/Sanofi, improves dyslipidemia, and reduces the risk of ASCVD in the phase II and III studies [12–14]. Recently, the inducible degrader of LDLR (IDOL) was identified as a novel post-transcriptional regulator of LDLR [15]. IDOL decreases LDLR abundance and attenuates LDL uptake into cells. These actions are very similar to the inhibitor of PCSK9. Although through different mechanisms, both PCSK9 and IDOL have been shown to modulate LDLR distribution in the cell surface and control the levels of LDL-C in serum. We therefore propose that IDOL may be a potential therapeutic target for the ASCVD by decreasing dyslipidemia (Fig. 1).

Hypothesis

Based on these exciting findings, we hypothesize that inhibition of IDOL function will increase LDLR expression in the liver cell and subsequently decrease the levels of serum LDL-C in dyslipidemic patients. Furthermore, the IDOL inhibitor will significantly reduce the risk of ASCVD.

Rationale for the hypothesis

IDOL involves in LDLR expression

The effect of the liver X receptor (LXR) agonists (GW3695 or T1317) on cholesterol uptake in human liver HepG2 cells and primary mouse macrophages was first reported by Zelcer et al. [15] in 2009. They have found that LXR ligands reduced the levels of LDLR protein but had little effect on LDLR mRNA. Further, these ligands reduced the binding and uptake of BODIPY-labeled LDL, which was independent of cellular sterol levels. A further linking endogenous LXR ligands and LDLR expression study revealed that the activated LXR decreased LDLR protein expression and redistributed proteins from the plasma membrane to cell organelles. Later, IDOL was identified as the myosin regulatory light chain interacting protein (MYLIP) [15,16].

IDOL serves as an E3-ubiquitin ligase

The human *Idol* gene is located in 6p23–p22.3 [17]. This gene encodes a 445 amino acid protein, which is identified as an E3-ubiquitin ligase containing an N-terminal frame of ezrin/radixin/-moesin homology (FERM) domain and a C-terminal catalytic really interesting new gene (RING) domain separated by a short linker region [18]. The FERM domain contains the F1, F2, and F3 subdomains with a phosphotyrosine-binding (PTB) domain embedded. The FERM domain mediates interaction with the cytoplasmic domains of transmembrane proteins, whereas the RING domain acts as an E3-ubiquitin ligase facilitating the direct transfer of ubiquitin from E2 to the substrate [18–20]. The E3 ligases have two main categories. One category contains HECT domain acting as a conjugation of ubiquitin by forming a HECT-ubiquitin intermediator, and the other has the RING domain that facilitates the direct transfer of ubiquitin from E2 to the substrate as an E3-ubiquitin ligase [18–20]. Sorrentino et al. [20] also pointed out that the RING domain promoted Lys-63-specific ubiquitination of the LDLR of HepG2 cells when treated with GW3965 and bafilomycin A (Fig. 2).

IDOL modulates the LDLR protein distribution

IDOL is regulated by LXRs which binds to the LXR element in the upstream of translation start site of IDOL and in responding to extracellular cholesterol levels. IDOL expression was induced by LXR agonists in many types of cells, including primary hepatocytes, macrophages, mouse embryonic fibroblasts (MEFs), and HepG2 cells, and its expression is also found in various tissues, such as the spleen, intestine, and adrenals [15]. Constitutive IDOL expression was detected in the liver of LXR$\alpha\beta^{-/-}$ mice compared with the wild-type controls, but IDOL still regulates LDLR protein expression and influences LDL uptake in cultured hepatocytes