The E3 ubiquitin ligase inducible degrader of the LDL receptor/myosin light chain interacting protein in health and disease

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Purpose of review
The RING E3 ubiquitin ligase inducible degrader of the LDL receptor (IDOL, also known as MYLIP) promotes ubiquitylation and subsequent lysosomal degradation of the LDL receptor (LDLR), thus acting to limit uptake of lipoprotein-derived cholesterol into cells. Next to the LDLR, IDOL also promotes degradation of two related receptors, the very LDL receptor (VLDLR) and apolipoprotein E receptor 2 (APOER2), which have important signaling functions in the brain. We review here the emerging role of IDOL in lipoprotein and energy metabolism, neurodegenerative diseases, and the potential for therapeutic targeting of IDOL.

Recent findings
Genetic studies suggest an association between *IDOL* and lipoprotein metabolism in humans. Studies in rodents and nonhuman primates support an in-vivo role for IDOL in lipoprotein metabolism, and also uncovered an unexpected role in whole-body energy metabolism. Recent evaluation of IDOL function in the brain revealed a role in memory formation and progression of Alzheimer's disease. The report of the first IDOL inhibitor may facilitate further investigations on therapeutic strategies to target IDOL.

Summary
IDOL is emerging as an important determinant of lipid and energy metabolism in metabolic disease as well as in Alzheimer's disease. IDOL targeting may be beneficial in treating these conditions.

Keywords
cholesterol metabolism, inducible degrader of the LDL receptor, lipoprotein receptors, metabolic syndrome, neurodegenerative disease

INTRODUCTION

Cholesterol metabolism has a well established role in development of cardiovascular disease, with an elevated level of circulating LDL representing a major risk factor for cardiovascular disease development. Lipoprotein metabolism is now recognized as an important determinant of other human maladies, including obesity and neurodegenerative diseases. This emphasizes the need to tightly coordinate lipoprotein metabolism at the cellular and organismal level, a process in which lipoprotein receptors play a crucial role.

The LDL receptor (LDLR), through its ability to enhance hepatic clearance of LDL from the circulation governs LDL metabolism [1,2]. Accordingly, mutations in the *LDLR* are the most frequent cause of familial hypercholesterolemia. It follows that the level and activity of the LDLR needs to be tightly controlled and for this both transcriptional and posttranscriptional mechanisms are used. Transcriptional regulation of the *LDLR* is primarily under control of the Sterol Regulatory Element-Binding Protein (SREBP) family of transcription factors [1,3,4]. Two potent posttranscriptional regulators of the LDLR that promote its lysosomal degradation have been described; the secreted proprotein convertase subtilisin/kexin type 9 (PCSK9) (for reviews see [5,6]), and the E3 ubiquitin ligase inducible degrader of the LDLR [IDOL, also known as the myosin light chain interacting protein (MYLIP)]

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Curr Opin Lipidol 2019, 30:192–197
DOI:10.1097/MOL.0000000000000593

KEY POINTS

- Variation in *IDOL* is associated with lipid traits in humans.
- Rodent and nonhuman primate models of *Idol/IDOL* demonstrate an in-vivo role in lipoprotein metabolism.
- Loss of *Idol* in mice improves metabolic regulation during normal physiological aging and in response to a high-fat diet.
- *Idol* is implicated in learning and memory formation.
- Loss of *Idol* in mice reduces Alzheimer's-disease-like symptoms.

[7,8]. Here, we cover recent advances in our understanding of IDOL function and its role in health and disease.

CLONING AND CHARACTERIZATION OF INDUCIBLE DEGRADER OF THE LDL RECEPTOR/MYOSIN LIGHT CHAIN INTERACTING PROTEIN

MYLIP (referred to further as *IDOL*) was cloned from a brain cDNA library in search of novel neuronal cytoskeletal regulators [9]. *IDOL* is ubiquitously expressed, with particular high expression in the hippocampus [10▪▪,11]. The molecular cloning of *IDOL* revealed it is a cytosolic protein of ~50 kDa (445 amino acids) that consists of two major protein domains; a C-terminal really interesting new gene (RING) domain and an N-terminal FERM domain. FERM domains are present in proteins, such as ezrin, radixin and moesin, and known to regulate plasma membrane–cytoskeleton interactions [12]. Accordingly, studies of IDOL's FERM domain indicated predominant localization to the plasma membrane [13]. The presence of the E3 ligase RING domain in IDOL is unique among human FERM proteins, and suggests that IDOL may influence the function or level of membrane proteins via targeted ubiquitination.

Ubiquitination – the conjugation of the small protein ubiquitin to target proteins – is a process requiring the sequential activity of an E1-activating, an E2-conjugating, and an E3-ligating enzyme [14]. Target specificity is largely dictated, in the case of RING E3s like IDOL, by the E3 ligase itself. In 2009, the LDLR was identified as a direct ubiquitination target of IDOL [7]. Together with the E2 UBC13 or members of the UBE2D E2 family [13,15], IDOL promotes ubiquitination of a conserved lysine residue in the short intracellular tail of the receptor, a mark that targets the LDLR for subsequent lysosomal degradation through a clathrin-independent pathway [16,17]. Expression of *IDOL* is transcriptionally regulated by the sterol-sensing liver X receptor (LXR) transcription factors [7]. LXRs are members of the ligand activated nuclear receptor family of transcription factors, and respond to elevated levels of oxysterols and intermediates of the biosynthetic pathway by increasing expression of their target genes, amongst them *IDOL* [18]. Induction of the LXR–IDOL axis leads to decreased LDLR protein and associated cellular LDL uptake, and as such its activation can be viewed as a feedback mechanism to prevent further cellular cholesterol accumulation when its levels are adequate (Fig. 1). Posttranscriptional regulation also plays an important role in controlling IDOL levels and activity, as similar to other E3 ligases, IDOL promotes its own auto-ubiquitylation and rapid proteasomal degradation [7,19▪▪]. Intriguingly, we have reported that degradation of the LDLR by IDOL is subject to negative regulation by the de-ubiquitinating enzyme USP2 [19▪▪]. It remains to be seen whether this is because of direct removal of ubiquitin from the LDLR, which redirects the receptor away from the degradation pathway, or that removal of ubiquitin from IDOL directly inhibits its activity.

In addition to the LDLR, IDOL also promotes ubiquitination-dependent degradation of the closely related receptors, the very LDL receptor (VLDLR) and apolipoprotein E receptor 2 (APOER2) [20], which are notably also targeted by PCSK9 [21]. These two receptors play an important role in the Reelin signaling pathway and are required during development for proper neuronal migration and positioning [22]. To date, no other ubiquitination targets have been conclusively established for IDOL. This narrow and specific target specificity is rather unique among E3s, as typically E3s are promiscuous and have a broader spectrum of ubiquitination targets. IDOL's specificity is dependent on recognition between the FERM domain and a conserved motif in the intracellular tail of the LDLR, VLDLR, and APOER2 [13,23▪], which is further enhanced by proper orientation of IDOL with the negatively charged surface of the plasma membrane [23▪]. Akin to the LDLR, genetic or pharmacologic manipulation of the LXR–IDOL axis regulates the level of the VLDLR and APOER2 [10▪▪,20]. However, whether cholesterol metabolism and LXRs are relevant physiological signals for regulating these receptors *in vivo* is unclear at present (see below). In view of its target specificity and the known functions of its targets in lipoprotein metabolism and neuronal function, IDOL has been studied in these contexts in recent years.

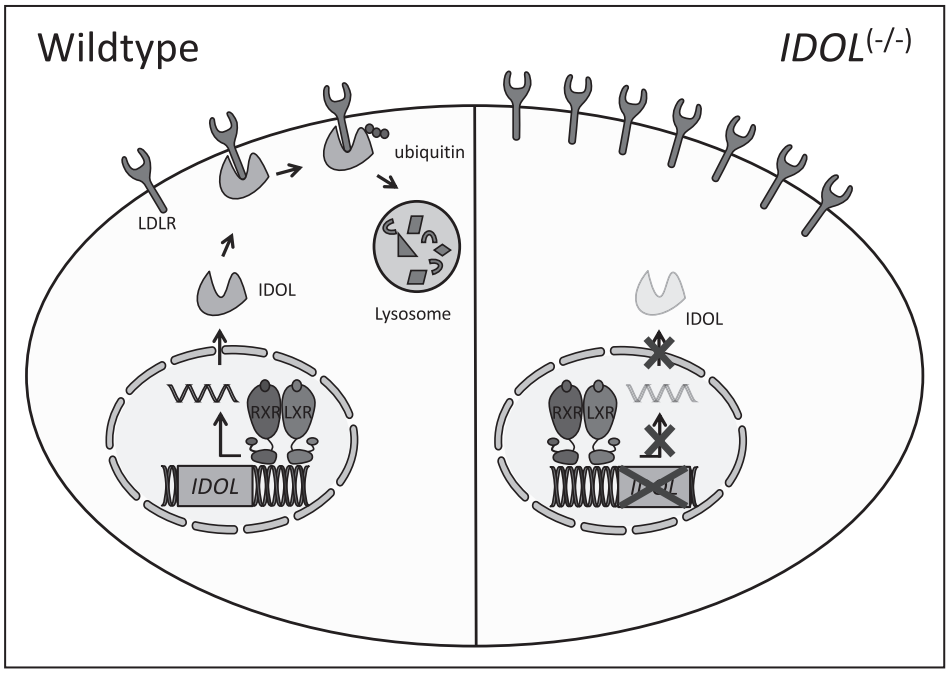

FIGURE 1. Schematic representation of the liver X receptor– inducible degrader of the LDL receptor–LDL receptor axis. (left) LXR activation leads to transcriptional induction of *IDOL* expression. IDOL binds to and promotes ubiquitination of the intracellular tail of the LDLR, resulting in lysosomal degradation of the receptor. (right) In the absence of *IDOL*, degradation of the LDLR does not take place and as a result the level of the receptor increases. LXR, liver X receptor; IDOL, inducible degrader of the LDL receptor; LDLR, LDL receptor.

THE ROLE OF INDUCIBLE DEGRADER OF THE LDL RECEPTOR IN LIPOPROTEIN AND ENERGY METABOLISM

The mechanism underlying regulation of the LDLR by IDOL has been extensively studied in cell-based systems and suggests an important role in regulation of lipoprotein metabolism *in vivo* [8]. This notion was supported early-on by genome-wide association studies (GWAS) that reported an association between genetic variation in *IDOL* and circulating LDL levels in humans [24–27]. One of the single nucleotide polymorphisms (SNPs) identified in these studies, rs9370867, which encodes an *IDOL* Asn342Sen variant, was subsequently shown to have a significant association with plasma cholesterol levels in a dyslipidemic Mexican population and to affect LDLR degradation *in vitro* [28]. However, this association was not observed in subsequent Brazilian, Italian, and Dutch cohorts [29–31], putting the significance of this variant in question. Genetic variation in *IDOL* has also been associated with the response to lipid-lowering statins in the Brazilian cohort, as well as in the JUPITER trial [32,33]. Yet a recent report suggests that for one of the reported *IDOL* SNPs (rs6924995), the association with statin response may be linked to the nearby long noncoding RNA *RP1-13D10.2* (*RP1*), and not to *IDOL* itself [34]. Additional genetic support for the potential role of IDOL in human lipoprotein metabolism comes from our studies in a Dutch cohort in which mutations in other cholesterol-related genes have been excluded [31]. In this study, we identified an *IDOL* loss-of-function variant in a limited number of carriers, which was associated with reduced levels of circulating LDL. Taken together, human genetic studies, although not conclusive, support the involvement of IDOL in human lipoprotein metabolism and its targeting in cholesterol-lowering strategies.

The development of *Idol* mouse models has greatly facilitated the study of its in-vivo functions. Several studies have demonstrated that transient or stable hepatic transgenic expression of *IDOL*/*Idol* dramatically increases LDL levels in mice and hamsters [7,35,36▪,37], and consequently can promote atherosclerosis development [35]. Similarly, increasing hepatic *IDOL* expression in nonhuman primates by pharmacological LXR activation increased circulating LDL levels in an *IDOL*-dependent manner [38]. Conversely, cell-based assays, including experiments conducted in *Idol*$^{(-/-)}$ mouse embryonic stem cells [39], demonstrated that loss of *IDOL* expression increases the level of the LDLR and concomitantly enhances LDL uptake [7,16,17]. However, different from these experiments, initial assessment of global loss of *Idol* in mice unexpectedly showed no significant effect on circulating total cholesterol or LDL-cholesterol [38]. This was proposed to be a result of

species-dependent hepatic IDOL activity; in mice, IDOL is highly active in peripheral tissues yet its activity in the liver is muted, whereas in nonhuman primates (and presumably humans [31]) hepatic IDOL activity is prominent. In line with this, antisense oligonucleotide (ASO)-based *IDOL* silencing increased hepatic LDLR and attenuated the rise in circulating levels of LDL following treatment with an LXR ligand in nonhuman primates [38]. However, in contrast to the initial report in mice [38], we have recently found a significant decrease in circulating cholesterol in high-fat-diet-fed *Idol* knock-out mice, emphasizing the need for further studies on the role of IDOL in lipoprotein metabolism *in vivo* [40▪▪,41]. Surprisingly, despite the potential involvement of IDOL in LDL metabolism, no studies have been reported to date on the role of *Idol* ablation or silencing in coronary artery disease.

Beyond cholesterol homeostasis, we recently addressed the role of IDOL in broader lipoprotein and energy metabolism [40▪▪]. Our study was the first to report that mice lacking *Idol* are protected from age-induced and diet-induced weight gain, have reduced circulating triglyceride levels, improved glycemic control, and decreased neutral lipids accumulation in the liver and brown adipose tissue compared with their wildtype controls. Protection from these metabolic syndrome-associated comorbidities was remarkably not a result of a marked increase in energy expenditure. Rather, we speculated that sustained brown-adipose activity and enhanced sympathetic signaling in this tissue may underlie the improved metabolic function of $Idol^{(-/-)}$ mice. We also observed an increase in locomotor activity in $Idol^{(-/-)}$ mice, and although our study was not designed to address this issue, this could suggest involvement of IDOL in regulation of metabolism through central nervous system circuitry (see below).

THE ROLE OF INDUCIBLE DEGRADER OF THE LDL RECEPTOR IN THE CENTRAL NERVOUS SYSTEM AND NEURODEGENERATIVE DISEASE

Cholesterol transport within the brain is primarily carried out by ApoE-containing lipoproteins. The finding that the ε4 isoform of *ApoE* is the most robust genetic risk factor for Alzheimer's disease in humans suggests that disturbed central cholesterol homeostasis has a causal role in its pathophysiology [42,43]. All three IDOL targets are ApoE receptors, expressed in the brain, and have an established role in transport of cholesterol in this organ. Accordingly, the level of these receptors is increased in the brain in the absence of *Idol* [10▪▪,44], in contrast to the lack of change in their levels in *Pcsk9* knockout mice [45]. In line with this, ablation of *Idol* reduced ApoE protein levels in the brain, beta-amyloid (Aβ) plaque deposition, and neuroinflammation in a mouse Alzheimer's disease model [44]. This beneficial outcome has been attributed to enhanced LDLR-mediated clearance of Aβ-carrying ApoE particles by resident microglia cells, yet the possibility that Aβ clearance across the brain–blood barrier was also increased was not evaluated [46]. Moreover, as functional learning and memory in the Alzheimer's disease setting was not reported it remains to be seen whether loss of IDOL improves these parameters (discussed in [47]).

The high expression of *Idol* in the hippocampus [10▪▪,11], may suggest an important role for IDOL in learning and memory formation. Neuronal expression of *Idol* has been recently reported to influence dendritic spinogenesis and spine morphogenesis [10▪▪]. This is because of the ability of IDOL to titrate the levels of ApoER2 and couple synaptic activity to Rac1 activation. This coupling, which results in cytoskeletal remodeling important for spine formation and dynamics, is reminiscent of the original report showing that *IDOL* over-expression can inhibit neurite outgrowth in the PC12 neuroendocrine cell line [9]. As a result, absence of *Idol* and dysregulation of ApoER2 levels leads to impaired long-term potentiation (a proxy for memory formation) in primary neurons and hippocampal slices, and impaired learning and memory formation in mice lacking *Idol*. This represents a potential detrimental consequence of dysregulated IDOL activity in neurons. In that respect, we have previously reported that sterol-dependent regulation of *Idol* expression in neurons is blunted in comparison to other cell types [20], suggesting that other signals or mechanism may be more important for this in this lineage. Indeed, neuronal activation [10▪▪], as well as pro-Nerve growth factor and brain-derived neurotrophic factor [48,49] seem to regulate *Idol* expression. The underlying transcriptional mechanism has not been addressed, but it may involve sterol-independent regulation of *IDOL,* as we have recently reported [50▪].

THERAPEUTIC TARGETING OF INDUCIBLE DEGRADER OF THE LDL RECEPTOR AND OUTLOOK

IDOL plays a role in multiple tissues and cell types, and our current understanding of IDOL function suggests that targeting its expression or activity could be therapeutically beneficial in regimens to treat hypercholesterolemia, metabolic syndrome-associated morbidities, and potentially also Alzheimer's disease (Fig. 2). The beneficial effect of *IDOL*-directed

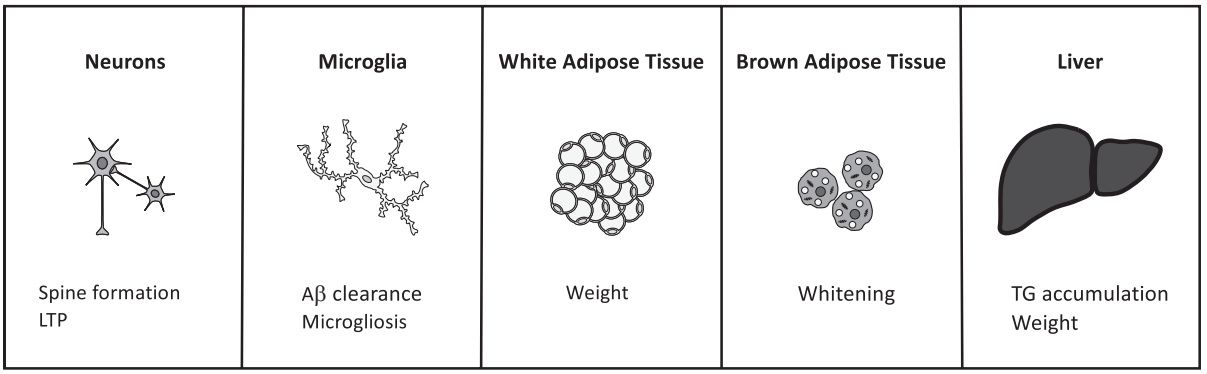

FIGURE 2. A summary of inducible degrader of the LDL receptor functions in physiological processes. IDOL function has been demonstrated to be important in the indicated cell types or tissues. In neurons, *Idol* has been shown to regulate ApoER2 levels and as a consequence affect spine formation, long-term potentiation and learning and memory formation [10▪▪]. In microglia, *Idol* ablation increases Aβ clearance and decreases microgliosis in a mouse model of Alzheimer's disease [44]. In liver, WAT, and BAT *Idol* ablation reduces high-fat-diet-induced fat accumulation and weight gain [40▪▪]. ApoER2, apolipoprotein E receptor 2; IDOL, inducible degrader of the LDL receptor.

ASOs in nonhuman primates demonstrates the feasibility of this approach [38], even though small-molecule IDOL inhibitors would be preferable. It is, therefore, encouraging that the first peptide-based inhibitor of IDOL, which interferes with its dimerization, has been reported [51▪]. Targeting the interaction between IDOL and its targets or its association with the membrane also offer opportunities to inhibit IDOL activity. Although challenging, availability of the high-resolution structure of IDOL will facilitate these developments. Given the strong effect *Idol* has on memory and learning in mice [10▪▪], caution should be taken during development of IDOL inhibitors. We point out that whereas the current focus lies in developing IDOL inhibitors, increasing IDOL activity may be a tractable approach to treat glioblastoma [52,53▪], and potentially other tumors, which are dependent on LDLR-mediated lipoprotein uptake. Despite an increase in our understanding of IDOL several pertinent questions remain:

(1) How does *Idol* loss improve metabolic syndrome-associated comorbidities and in which tissue(s) is IDOL activity pertinent for this? Importantly, does this translate to the human setting?
(2) How is *IDOL* transcriptionally regulated in different cell types and tissues?
(3) What is the consequence of IDOL inhibition or ablation on atherosclerosis?
(4) What is the specific contribution of each of the three IDOL targets to its overall in-vivo function?
(5) Can effective and safe small-molecule inhibitors be developed for in-vivo use and can these inhibitors act either independently or complementary to statins and PCSK9 inhibitors?
(6) Is IDOL involved in learning and memory disabilities in humans?

For addressing some of these questions, generation of tissue-specific *Idol* models will be instrumental. The growing interest in therapeutic targeting of IDOL and the recent description of the first pharmacological IDOL inhibitor ensure that the coming years of IDOL research will be exciting ones.

Acknowledgements

We thank Irith Koster for the critical reading of this review.

Financial support and sponsorship

D.L. Supported by Finska Läkaresällskapet, the Novo Nordisk Foundation, the Magnus Ehrnrooth, Liv and Hälsa Foundation, the Minerva Foundation, and the Academy of Finland. N.Z. is an established investigator of the Dutch Heart Foundation (2013T111) and is supported by a European Research Council Consolidator grant (617376) from the European Research Council and by a Vici grant from the Netherlands Organization for Scientific Research (NWO; 016.176.643).

Conflicts of interest

There are no conflicts of interest.

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