



# 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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## 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.

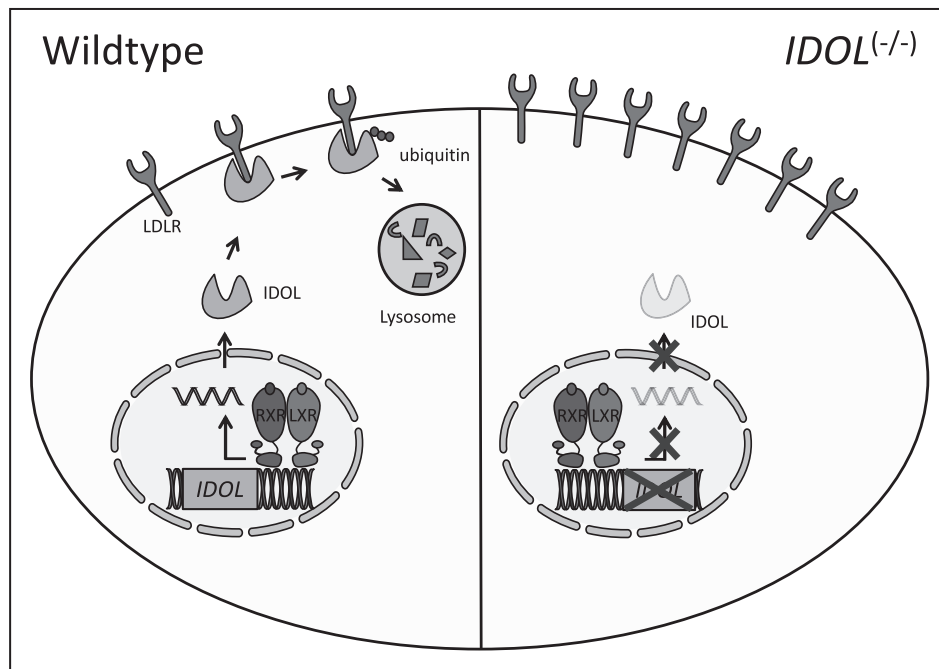
## CLONING AND CHARACTERIZATION OF INDUCIBLE DEGRADER OF THE LDL RECEPTOR/MYOSIN LIGHT CHAIN INTERACTING PROTEIN

*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<sup>11</sup>]. 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<sup>22</sup>]. Intriguingly, we have reported that degradation of the LDLR by *IDOL* is subject to negative regulation by the de-ubiquitinating enzyme USP2 [19<sup>22</sup>]. 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<sup>24</sup>], which is further enhanced by proper orientation of *IDOL* with the negatively charged surface of the plasma membrane [23<sup>24</sup>]. Akin to the LDLR, genetic or pharmacologic manipulation of the LXR–*IDOL* axis regulates the level of the VLDLR and APOER2 [10<sup>22</sup>,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* Asn342Ser 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*<sup>(-/-)</sup> 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<sup>\*\*\*</sup>,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<sup>\*\*\*</sup>]. 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*<sup>(-/-)</sup> mice. We also observed an increase in locomotor activity in *Idol*<sup>(-/-)</sup> 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

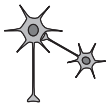
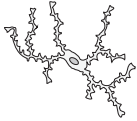



Cholesterol transport within the brain is primarily carried out by ApoE-containing lipoproteins. The finding that the  $\epsilon 4$  isoform of *ApoE* is the most robust genetic risk factor for Alzheimer's disease in humans suggests that disturbed central cholesterol homeostasis has a causal role in 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<sup>\*\*\*</sup>,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 (A $\beta$ ) plaque deposition, and neuroinflammation in a mouse Alzheimer's disease model [44]. This beneficial outcome has been attributed to enhanced LDLR-mediated clearance of A $\beta$ -carrying ApoE particles by resident microglia cells, yet the possibility that A $\beta$  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<sup>\*\*\*</sup>,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<sup>\*\*\*</sup>]. 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<sup>\*\*\*</sup>], 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<sup>\*</sup>].

### 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

Neurons	Microglia	White Adipose Tissue	Brown Adipose Tissue	Liver
				
Spine formation LTP	A $\beta$ clearance Microgliosis	Weight	Whitening	TG accumulation Weight

**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<sup>10</sup>]. In microglia, *Idol* ablation increases A $\beta$  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<sup>10</sup>]. 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<sup>10</sup>]. 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<sup>10</sup>], 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<sup>10</sup>], 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.

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### Conflicts of interest

There are no conflicts of interest.

### REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* 2015; 161:161–172.

2. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986; 232:34–47.
3. Yokoyama C, Wang X, Briggs MR, *et al.* SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low density lipoprotein receptor gene. *Cell* 1993; 75:187–197.
4. Hua X, Yokoyama C, Wu J, *et al.* SREBP-2, a second basic-helix-loop-helix-leucine zipper protein that stimulates transcription by binding to a sterol regulatory element. *Proc Natl Acad Sci U S A* 1993; 90:11603–11607.
5. Seidah NG, Awan Z, Chretien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. *Circ Res* 2014; 114:1022–1036.
6. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. *J Lipid Res* 2009; 50(Suppl):S172–S177.
7. Zelcer N, Hong C, Boyadjian R, Tontonoz P. LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. *Science* 2009; 325:100–104.
8. Sorrentino V, Zelcer N. Posttranscriptional regulation of lipoprotein receptors by the E3-ubiquitin ligase inducible degrader of the low-density lipoprotein receptor. *Curr Opin Lipidol* 2012; 23:213–219.
9. Olsson PA, Korhonen L, Mercer EA, Lindholm D. MIR is a novel ERM-like protein that interacts with myosin regulatory light chain and inhibits neurite outgrowth. *J Biol Chem* 1999; 274:36288–36292.
10. Gao J, Marosi M, Choi J, *et al.* The E3 ubiquitin ligase IDOL regulates synaptic ApoER2 levels and is important for plasticity and learning. *Elife* 2017; 6:1741. This recent study demonstrates that IDOL controls the level of the ApoER2 receptor and as a result dendritic spine morphogenesis in neurons. As a consequence, loss of Idol impairs plasticity and memory formation.
11. Olsson PA, Bornhauser BC, Korhonen L, Lindholm D. Neuronal expression of the ERM-like protein MIR in rat brain and its localization to human chromosome 6. *Biochem Biophys Res Commun* 2000; 279:879–883.
12. Fehon RG, McClatchey AI, Bretscher A. Organizing the cell cortex: the role of ERM proteins. *Nat Rev Mol Cell Biol* 2010; 11:276–287.
13. Sorrentino V, Scheer L, Santos A, *et al.* Distinct functional domains contribute to degradation of the low density lipoprotein receptor (LDLR) by the E3 ubiquitin ligase inducible Degradator of the LDLR (IDOL). *J Biol Chem* 2011; 286:30190–30199.
14. Ciechanover A. Intracellular protein degradation: from a vague idea through the lysosome and the ubiquitin-proteasome system and onto human diseases and drug targeting. *Neurodegener Dis* 2012; 10:7–22.
15. Zhang L, Fairall L, Goult BT, *et al.* The IDOL-UBE2D complex mediates sterol-dependent degradation of the LDL receptor. *Genes Dev* 2011; 25:1262–1274.
16. Scotti E, Calamai M, Goulbourne CN, *et al.* IDOL stimulates clathrin-independent endocytosis and multivesicular body-mediated lysosomal degradation of the low-density lipoprotein receptor. *Mol Cell Biol* 2013; 33:1503–1514.
17. Sorrentino V, Nelson JK, Maspero E, *et al.* The LXR-IDOL axis defines a clathrin-, caveolae-, and dynamin-independent endocytic route for LDLR internalization and lysosomal degradation. *J Lipid Res* 2013; 54:2174–2184.
18. Hong C, Tontonoz P. Liver X receptors in lipid metabolism: opportunities for drug discovery. *Nat Rev Drug Discov* 2014; 13:433–444.
19. Nelson JK, Sorrentino V, Avagliano Trezza R, *et al.* The deubiquitylase USP2 regulates the LDLR pathway by counteracting the E3-Ubiquitin Ligase IDOL. *Circ Res* 2016; 118:410–419. Here, the de-ubiquitinase USP2 is identified as a negative regulator of IDOL-mediated degradation of the LDLR.
20. Hong C, Duit S, Jalonen P, *et al.* The E3 ubiquitin ligase IDOL induces the degradation of the low density lipoprotein receptor family members VLDLR and ApoER2. *J Biol Chem* 2010; 285:19720–19726.
21. Poirier S, Mayer G, Benjannet S, *et al.* The proprotein convertase PCSK9 induces the degradation of low density lipoprotein receptor (LDLR) and its closest family members VLDLR and ApoER2. *J Biol Chem* 2008; 283:2363–2372.
22. Lane-Donovan C, Herz J. The ApoE receptors Vldlr and Apoer2 in central nervous system function and disease. *J Lipid Res* 2017; 58:1036–1043.
23. Calkin AC, Goult BT, Zhang L, *et al.* FERM-dependent E3 ligase recognition is a conserved mechanism for targeted degradation of lipoprotein receptors. *Proc Natl Acad Sci USA* 2011; 108:20107–20112. Together with reference [13], this study defines the molecular interactions between the IDOL FERM domain and the intracellular tail of the LDLR.
24. Chasman DI, Paré G, Mora S, *et al.* Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. *PLoS Genet* 2009; 5:e1000730.
25. Teslovich TM, Musunuru K, Smith AV, *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010; 466:707–713.
26. Waterworth DM, Ricketts SL, Song K, *et al.* Genetic variants influencing circulating lipid levels and risk of coronary artery disease. *Arterioscler Thromb Vasc Biol* 2010; 30:2264–2276.
27. Willer CJ, Schmidt EM, *et al.* Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013; 45:1274–1283.
28. Weissglas-Volkov D, Calkin AC, Tusie-Luna T, *et al.* The N342S MYLIP polymorphism is associated with high total cholesterol and increased LDL receptor degradation in humans 2011; 121:3062–3071.
29. Santos PCJL, Oliveira TGM, Lemos PA, *et al.* MYLIP p.N342S polymorphism is not associated with lipid profile in the Brazilian population. *Lipids Health Dis* 2012; 11:83.
30. Dhyani A, Tibolla G, Baragetti A, *et al.* IDOL N342S variant, atherosclerosis progression and cardiovascular disorders in the Italian general population. *PLoS One* 2015; 10:e0122414.
31. Sorrentino V, Fouchier SW, Motazacker MM, *et al.* Identification of a loss-of-function inducible degrader of the low-density lipoprotein receptor variant in individuals with low circulating low-density lipoprotein. *Eur Heart J* 2013; 34:1292–1297.
32. Santos PCJL, Morgan AC, Jannes CE, *et al.* The MYLIP p.N342S polymorphism is associated with response to lipid-lowering therapy in Brazilian patients with familial hypercholesterolemia. *Pharmacogenet Genom* 2014; 24:548–555.
33. Chasman DI, Giulianini F, Macfadyen J, *et al.* Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) trial. *Circ Cardiovasc Genet* 2012; 5:257–264.
34. Mitchel K, Theusch E, Cubitt C, *et al.* RP1-13D10.2 is a novel modulator of statin-induced changes in cholesterol. *Circ Cardiovasc Genet* 2016; 9:223–230.
35. Calkin AC, Lee SD, Kim J, *et al.* Transgenic expression of dominant-active IDOL in liver causes diet-induced hypercholesterolemia and atherosclerosis in mice. *Circ Res* 2014; 115:442–449.
36. Ibrahim S, Somanathan S, Billheimer J, *et al.* Stable liver-specific expression of human IDOL in humanized mice raises plasma cholesterol. *Cardiovasc Res* 2016; 110:23–29. Similar to [35], this study uses AAV-IDOL as a model to evaluate hepatic IDOL activity.
37. Sasaki M, Terao Y, Ayaori M, *et al.* Hepatic overexpression of idol increases circulating protein convertase subtilisin/kexin type 9 in mice and hamsters via dual mechanisms: sterol regulatory element-binding protein 2 and low-density lipoprotein receptor-dependent pathways. *Arterioscler Thromb Vasc Biol* 2014; 34:1171–1178.
38. Hong C, Marshall SM, McDaniel AL, *et al.* The LXR-Idol axis differentially regulates plasma LDL levels in primates and mice. *Cell Metab* 2014; 20:910–918.
39. Scotti E, Hong C, Yoshinaga Y, *et al.* Targeted disruption of the idol gene alters cellular regulation of the low-density lipoprotein receptor by sterols and liver x receptor agonists. *Mol Cell Biol* 2011; 31:1885–1893.
40. van Loon NM, Ottenhoff R, Kooijman S, *et al.* Inactivation of the E3 ubiquitin ligase IDOL (inducible degrader of the low-density lipoprotein receptor) attenuates diet-induced obesity and metabolic dysfunction in mice. *Arterioscler Thromb Vasc Biol* 2018; 38:1785–1795. This recent study implicates IDOL in whole-body lipid and energy metabolism and demonstrates that loss of IDOL protects against age-induced and diet-induced metabolic alterations.
41. van Loon NM, Rensen PCN, Zelcer N. IDOL in metabolic, neurodegenerative and cardiovascular disease. *Aging (Albany NY)* 2018; 10:3042–3043.
42. Chang TY, Yamauchi Y, Hasan MT, Chang C. Cellular cholesterol homeostasis and Alzheimer's disease. *J Lipid Res* 2017; 58:2239–2254.
43. Huynh T-PV, Davis AA, Ulrich JD, Holtzman DM. Apolipoprotein E and Alzheimer's disease: the influence of apolipoprotein E on amyloid- $\beta$  and other amyloidogenic proteins. *J Lipid Res* 2017; 58:824–836.
44. Choi J, Gao J, Kim J, *et al.* The E3 ubiquitin ligase Idol controls brain LDL receptor expression, ApoE clearance, and A $\beta$  amyloidosis. *Sci Transl Med* 2015; 7:314ra184–314ra324.
45. Liu M, Wu G, Baysarowich J, *et al.* PCSK9 is not involved in the degradation of LDL receptors and BACE1 in the adult mouse brain. *J Lipid Res American Society for Biochemistry and Molecular Biology* 2010; 51:2611–2618.
46. Castellano JM, Deane R, Gottesdiener AJ, *et al.* Low-density lipoprotein receptor overexpression enhances the rate of brain-to-blood A $\beta$  clearance in a mouse model of  $\beta$ -amyloidosis. *Proc Natl Acad Sci USA* 2012; 109:15502–15507.
47. Van Loon NM, Zelcer N. Idolizing the clearance of Amyloid- $\beta$  by microglia. *Ann Transl Med* 2016; 4:536–546.
48. Do HT, Bruelle C, Tselykh T, *et al.* Reciprocal regulation of very low density lipoprotein receptors (VLDLRs) in neurons by brain-derived neurotrophic factor (BDNF) and Reelin: involvement of the E3 ligase Mylip/Idol. *J Biol Chem* 2013; 288:29613–29620.
49. Do HT, Bruelle C, Pham DD, *et al.* Nerve growth factor (NGF) and pro-NGF increase low-density lipoprotein (LDL) receptors in neuronal cells partly by different mechanisms: role of LDL in neurite outgrowth. *J Neurochem* 2015; 136:306–315.
50. Nelson JK, Cook ECL, Loregger A, *et al.* Deubiquitylase inhibition reveals liver x receptor-independent transcriptional regulation of the E3 ubiquitin ligase IDOL and lipoprotein uptake. *J Biol Chem* 2016; 291:4813–4825. This report identifies an LXR-independent mechanism to regulate IDOL expression.
51. Leitch EK, Elumalai N, Fridén-Saxin M, *et al.* Inhibition of low-density lipoprotein receptor degradation with a cyclic peptide that disrupts the homodimerization of IDOL E3 ubiquitin ligase. *Chem Sci* 2018; 9:5957–5966. The first peptide-based IDOL inhibitor is described in this study.
52. Guo D, Reinitz F, Youssef M, *et al.* An LXR agonist promotes GBM cell death through inhibition of an EGFR/AKT/SREBP-1/LDLR-dependent pathway. *Cancer Discov* 2011; 1:442–456.
53. Villa GR, Hulce JJ, Zanca C, *et al.* An LXR-cholesterol axis creates a metabolic co-dependency for brain cancers. *Cancer Cell* 2016; 30:683–693. Together with [52], this study demonstrates that activation of the LXR-IDOL axis may be beneficial in the setting of glioblastoma.