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LIPID METABOLISM

An 'IDOL' regulator of blood cholesterol levels

Low-density lipoprotein receptor (LDLR) is crucial for maintaining levels of LDL — the so-called 'bad' form of cholesterol — by binding and facilitating the cellular uptake of LDL and thereby lowering its level in the bloodstream. Indeed, elevated levels of LDL in circulation can lead to medical conditions such as heart disease, stroke and clogged arteries. Zelcer *et al.* now report on a new mechanism of LDLR regulation by IDOL (inducible degrader of the LDLR), an E3 ubiquitin ligase that targets LDLR for degradation.

The authors initially questioned whether the liver X receptors (LXRs), which are known to regulate intracellular levels of cholesterol, can also modulate LDL uptake. After treating human liver and mouse macrophage cells with an LXR ligand, they observed a decrease in protein, but not mRNA, levels of LDLR. To understand how LXR regulates LDLR, the authors examined transcriptional target genes of LXR and identified a gene that encodes a myosin interacting protein, IDOL. IDOL contains a functional domain that mediates an interaction with the cytoplasmic domains of transmembrane proteins and a carboxy-terminal RING domain, which is known to have ubiquitin ligase activity.

> "…IDOL mediates the ubiquitylation and degradation of LDLR…"

Using *in vitro* assays, the authors observed that IDOL expression causes the redistribution of LDLR from the plasma membrane to an intracellular compartment and showed that IDOL mediates the ubiquitylation and degradation of LDLR through the lysosomal pathway. IDOL can even mediate the degradation of the receptor precursor in the endoplasmic reticulum.

To further investigate the effect of the LXR–IDOL pathway *in vivo*, the authors treated mice with a synthetic LXR ligand and observed induced IDOL expression, which corresponds to reduced LDLR protein levels. Functionally, forced IDOL expression markedly reduces LDLR expression, resulting in increased plasma cholesterol. Together, these results suggest that LXR can control cholesterol homeostasis through regulating IDOL expression and eliciting IDOL-mediated LDLR degradation *in vivo*. Further work is needed to show the requirement for IDOL in LDLR degradation *in vivo* and how to exploit IDOL as a potential therapeutic target for lowering cholesterol levels.

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ORIGINAL RESEARCH PAPER Zelcer, N. *et al.* LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. *Science* 11 Jun 2009 (doi:10.1126/science.1168974)