New Idol for Cholesterol Reduction?
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The discovery of the statins was a great success in cardiovascular research and pharmaceutical development. It was the answer to the epidemiologic problem that higher plasma cholesterol concentrations were associated with a higher occurrence of coronary artery disease (CAD) events. The statins inhibit a rate-limiting enzyme of cholesterol synthesis, hydroxymethylglutaryl (HMG)-CoA reductase, and consequently reduce the plasma LDL cholesterol concentration. Clinical trials proved the lower the better law for cholesterol as long as statins are used. This success pushed various kinds of cholesterol-reducing agents into the pipelines of pharmaceutical companies. Those cholesterol-reducing drugs that followed statins were cholesteryl ester transporter protein (CETP) inhibitors, Niemann–Pick C1-like 1 (NPC1L1) inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors, and acyl-CoA cholesterol acyltransferase (ACAT) inhibitors. These chemicals effectively reduced plasma LDL through different modes of action from statins.

Agents that increase the number of LDL receptors (LDLRs) were once sought. One such agent, estrogen, while being an endogenous molecule, was shown to actually exhibit antiatherogenic effects in part by increasing LDLRs in liver and thus decreasing LDL in plasma. In the July 3, 2009, issue of Science, Zelcer et al. (1) reported to have found a new mechanism to regulate the number of LDLRs, which would be a drug target to control LDL. The molecule Idol (inducible degrader of LDLRs) that they found might be a molecular target for such a strategy.

Intracellular Regulation of Cholesterol Level

Two major transcriptional mechanisms to regulate cholesterol are the pathways mediated by sterol responsive element–binding protein (SREBP) and liver X receptor (LXR), which tightly regulate intracellular sterol concentrations (Fig. 1).

The response to the reduction of intracellular sterol is mediated by transcription factor SREBP (2). SREBP is a transmembrane protein localized in the endoplasmic reticulum (ER), in complex with SREBP cleavage–activating protein (SCAP), which senses cholesterol. SCAP is further in complex with another sterol-sensing protein, insulin-induced gene 1 (INSIG1), to be tethered to ER. When the intracellular cholesterol concentration decreases, the SREBP/SCAP complex moves to Golgi apparatus, leaving INSIG. Two proteases localized in Golgi, site-1 and -2 proteases (S1P and S2P), then cleave SREBP to release the transcription activation domain of SREBP. SREBP activates transcription of target genes including LDLR. Although statins inhibit cholesterol synthesis, their major effects on plasma LDL are thought to be mediated by the upregulation of LDLR, since patients with homozygous familial hypercholesterolemia who completely lack LDLRs do not respond well to statins compared with heterozygotes. In other words, statins need upregulation of LDLRs for their reducing effects on plasma LDL. The effect is caused by negative feedback mechanism via SREBP, sensing the reduction of the intracellular cholesterol pool induced by the inhibition of HMG-CoA reductase.

Conversely, the response to excess cellular cholesterol is mediated by LXRs. LXRs target genes such as ABCA1 and ABCG1 [ATP-binding cassette transporter (ABC) A1 and G1] to promote the efflux of cellular cholesterol, which induces hepatic excretion of cholesterol into bile, suppression of intestinal cholesterol absorption, and enhancement of cholesterol reverse transport in peripheral cells. This indicates that LXR agonists are an ideal medication for the prevention of atherosclerosis. In mice, LXR agonists actually suppress atherosclerosis. Unfortunately, LXR agonists
induce hypertriglyceridemia, which is attributed to fatty acid synthesis enhanced by SREBP1c located downstream of LXRα. Pharmaceutical companies are now developing LXRα-selective agonists that do not induce SREBP1c and hence do not cause hypertriglyceridemia, while keeping their action of inducing ABCA1 and ABCG1.

Identification of Idol

In their recent report, Zelcer et al. noticed that LXR agonists control the uptake of LDL as well as efflux of cholesterol (1). LXR agonists suppress the uptake of LDL by decreasing LDLR proteins rather than mRNA. Because the change is not due to transcriptional control of the LDLR gene, it seems to be an indirect posttranslational effect of LXR agonists. Therefore, they searched for a molecule that directly decreases LDLR proteins among the target genes of LXR and found a molecule, designated Idol, that showed such ability. Idol has a RING domain characteristic of E3 ubiquitin ligase. E3 ubiquitin ligase is an enzyme that catalyzes covalent binding of multiple ubiquitin proteins to its substrates and enhances degradation of the substrate proteins in the proteasome. Idol actually demonstrated ubiquitination activity against LDLR. As known in other ubiquitinated proteins, the ubiquitinated LDLR is susceptible to degradation. Although ubiquitinated proteins are commonly degraded in the proteasome, in the case of LDLR it is degraded in the lysosome. Idol expression responds well to LXR agonists in peripheral organs such as the spleen, adrenal gland, and intestine, whereas without LXR agonist stimulation Idol expression is already high in the liver, although it still responds to LXR agonists. Interestingly, overexpression of Idol in mice significantly raises plasma cholesterol concentrations, especially LDL cholesterol, as if the mice were lacking LDLR, suggesting that the LXR-Idol-LDLR axis actually works in vivo. In LDLR-knockout mice, such effects of Idol are not observed, since they already lack LDLR.

These results are a reminder of the regulation of LDLR by proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is secreted into plasma and binds to EGF-A, the first domain of epidermal growth factor (EGF)-precursor homology repeats of LDLR. Although PCSK9 is a protease, it does not cleave LDLR, nor is the proteolysis of LDLR required to downregulate LDLR. By unknown mechanisms, binding of PCSK9 induces internalization and degradation of LDLR in the lysosome. Although no evidence exists, it is possible that PCSK9 binding to LDLR is an upstream event leading to ubiquitination of LDLR by Idol, judging from the similarity of their action on LDLR (Fig. 1). In other words, Idol may selectively ubiquitinate LDLR bound by PCSK9 to degrade, discriminating the LDLR-PCSK9 complex from LDLR in recycling pathway.

The More LDLRs the Better Strategy

The findings of Zelcer’s group have opened the possibility of anti-Idol therapy to reduce plasma LDL, although we must wait for results showing whether Idol
downregulation decreases plasma LDL concentrations in vivo as a result of LDLR upregulation. We also need to know more about the specificity of Idol. Zelcer’s team has shown that Idol does not affect protein concentrations of ABCA1, transferrin receptor, or some LDLR family proteins, i.e., lipoprotein receptor–related protein 4 (LRP4), sorting protein–related receptor (SorLA), and apolipoprotein E receptor (ApoER). However, it is natural to think that Idol has some protein substrate other than LDLR. In the case of statins, pleiotropic effects bring salutary effects on the body. The pleiotropic effects of statins are mainly owed to the inhibition of metabolic pathway of mevalonic acid. Statins decrease the products of the mevalonate pathway, including geranylgeranylphosphate, which is required for the activity of small G-proteins (3). Therefore, statins indirectly inhibit small G-protein activities. Fortunately, these unintended effects of statins are beneficial for health. Actually, their beneficial effects on vascular complication of the inhibitors for small G-proteins Rho and Rac signal transduction pathways have been reported (4). However, other types of LDL-reducing drugs are not blessed with such salutary actions as statins. Some serious adverse off-target effects have been observed. ACAT inhibitors cause adrenal toxicity. A CETP inhibitor, torcetrapib, induces hypertension in some patients. Therefore, to know the specificity of Idol is essential for its possibility as a target for cholesterol reduction.

Given that Idol is very specific to LDLR, and that a selective Idol inhibitor may be developed, it could be a promising therapeutic for dyslipidemia, since such a drug would trace the success model of statins in a sense. As described above, statins show their cholesterol-reducing effects basically by transcriptional upregulation of LDLR. Idol inhibitor would also increase LDLR by suppressing protein degradation. Furthermore, the difference of the upregulation mechanisms between statins and Idol inhibitors suggests that their combined use might bring in synergistic effects to increase LDLR. Idol inhibitor would stabilize the LDLR protein transcriptionally induced by statins, resulting in the enhancement of the action of statins. It may also be beneficial to use Idol inhibitor with LXRβ agonists. As described above, LXRβ-selective agonists increase cholesterol efflux without increase in triglyceride, but are still thought to decrease LDLR via the action of Idol. Idol inhibitor would suppress the LDLR-decreasing action of LXR agonists, without affecting beneficial action of LXR to increase cholesterol efflux. Developing Idol inhibitor is still a challenge, since no inhibitors for E3-ubiquitin ligases have yet been developed.

In the case of PCSK9, which is located in the LDLR degradation pathway, its gain-of-function mutations induce an autosomal dominant form of familial hypercholesterolemia in humans by reducing LDLRs. Its loss-of-function mutations increase LDLRs and reduce plasma LDL. Importantly, a loss-of-function mutation of PCSK9 decreasing LDL cholesterol by approximately 28% dramatically reduces cardiovascular disease (CVD) risk by 88% (5). Another mutation of PCSK9 decreasing plasma LDL by approximately 15% also reduces CVD risk by 47%. These are much more effective than the 5-year treatment with statins to the same degree of cholesterol reduction, suggesting that lifetime reduction of LDL should bring profound beneficial effects on the cardiovascular system. Furthermore, infusion of anti-PCSK9 monoclonal antibody, which blocks PCSK9-LDLR binding, increases LDLRs and reduces LDL by 80% in nonhuman primate carrying genetically normal PCSK9, indicating that we could intervene in the PCSK9-mediated pathway to increase LDLRs.

Thus, an LDLR-degrading pathway inhibitor would accurately target the same molecule LDLR as statins do, but in a manner different from that of statins. Although there still remains much to be explored on this new Idol, it doubtlessly holds enormous potentialities and may establish its place among pharmaceuticals as a target for developing new drugs for the treatment of dyslipidemia.

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