AUP1 (Ancient Ubiquitous Protein 1)

A Molecular Link Between Hepatic Lipid Mobilization and VLDL Secretion

Adil Mardinoglu, Jan Borén

Cardiovascular disease remains the leading cause of death around the world.[1] A major cause is atherogenic dyslipidemia, which is characterized by increased concentrations of triglyceride-rich lipoproteins and is seen in subjects with obesity and type 2 diabetes mellitus. Increased hepatic secretion of triglyceride-rich very-low-density lipoproteins (VLDL) is a major determinant of the hypertriglyceridemia.[2] The production of VLDL from the liver is a complex process. It starts with the formation of nascent lipoprotein particles that are further lipidated in the secretory pathway, resulting in the generation of triglyceride-rich VLDL particles that are secreted from the liver.[3] It is therefore not surprising that VLDL secretion—and thus the concentration of plasma triglycerides—is highly dependent on the availability of hepatic lipids.[4,5]

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Cellular lipids are stored in lipid droplets (LDs) consisting of a core of neutral lipids (mainly triglycerides and cholesteryl esters), surrounded by phospholipids and proteins.[3] Both lipids and proteins are synthesized in a membranous structure of the cell called the endoplasmic reticulum (ER). The ER compartment is also involved in quality control, as it identifies misfolded proteins that are degraded through ER-associated degradation or autophagic degradation.[6]

Interestingly, recent studies have shown that LDs are not only involved in lipid storage but are also important for proteasomal protein degradation and autophagy.[7] The AUP1 (ancient ubiquitous protein 1) was identified as the first LD-associated protein involved in ER-associated degradation.[7] The carboxyl terminus of AUP1 binds the E2 ubiquitin conjugases.[8] Thus, AUP1 provides a direct molecular link between LDs and ubiquitination-mediated degradation of misfolded ER proteins. In addition, AUP1 also controls lipid synthesis as it induces ubiquitination and the subsequent degradation of several key regulators of lipid biosynthesis, such as the cholesterol biosynthetic enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[9] The expression of AUP1, therefore, affects the amount and size of LDs. Thus, AUP1 has dual roles in protein quality control and LD regulation.[7]

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology,* Zhang et al[10] significantly extend these studies and for the first time demonstrated that AUP1 is a key determinant of hepatic VLDL assembly and secretion. AUP1 was found to interact with apolipoprotein B_{100} (apo B_{100}), and suppression of AUP1 increased triglyceride biosynthesis and the average size of cytosolic LDs, decreased post-translational degradation of apoB100, and enhanced section of mature triglyceride-rich VLDL from the human hepatoma cells HepG2 (Figure). These cells normally secrete smaller underlipidated apoB-containing lipoproteins instead of fully lipidated VLDL particles, and suppression of AUP1corrected this metabolic defect. Thus, AUP1 plays critical roles in intracellular lipid metabolism, apoB stability, and VLDL assembly and secretion.

How does suppression of AUP1 correct the defective VLDL assembly in HepG2 cells? The conversion of triglyceride-poor to triglyceride-rich VLDL has been proposed to require a bulk addition of triglycerides derived from cytosolic LDs.[11–14] Thus, it could be hypothesized that to retain lipids intracellularly instead of secreting triglyceride-rich VLDL, HepG2 hepatoma cells overexpress AUP1, which accumulates on LDs in the later part of the secretory pathway. Accumulation of AUP1 in LDs would hamper VLDL assembly.

Does AUP1 play a physiological role in VLDL secretion in nonhepatoma cells? This was not analyzed in this study. However, the expression of AUP1 has been measured in human liver samples obtained from a separate cohort of 12 obese subjects with increased liver fat content who underwent bariatric surgery,[15] and compared with AUP1 gene expression in liver samples obtained from 7 healthy individuals.[16] This comparison showed that the mRNA expression of AUP1 was significantly lower in liver from obese subjects than from healthy subjects (adjusted P value <0.05). These results may indicate that the regulation of AUP1 is impaired in subjects with nonalcoholic fatty liver disease and type 2 diabetes mellitus. Future studies are needed to address this in detail and to clarify whether AUP1 is linked to the altered hepatic lipid metabolism and increased VLDL secretion seen in subjects with nonalcoholic fatty liver disease and type 2 diabetes mellitus. If this turns out to be the case, AUP1 might become a drug target for preventing the diabetic dyslipidemia.

Disclosures

None.

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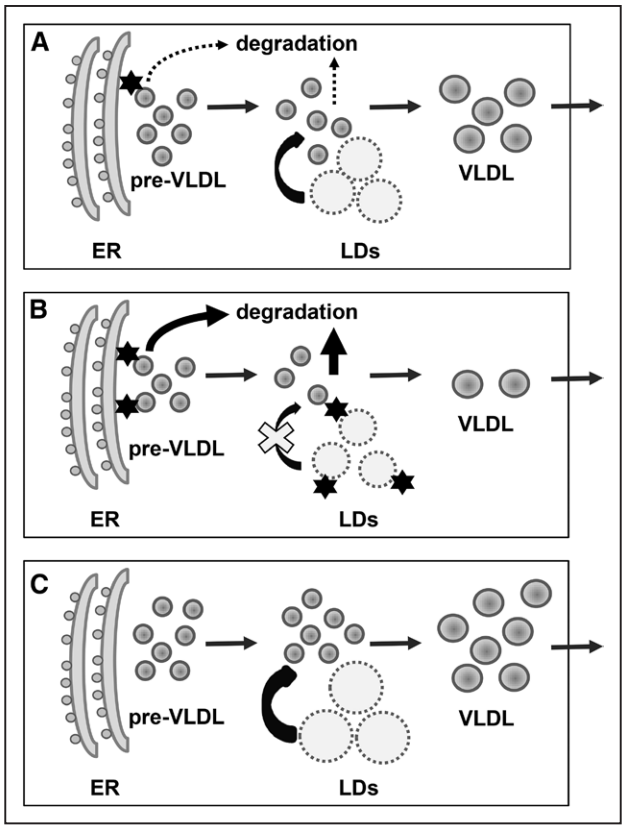

Figure. Impact of AUP1 (ancient ubiquitous protein 1) on lipid biogenesis and very low-density lipoproteins (VLDL) assembly. **A**, ApoB is synthesized and cotranslationally lipidated to form a pre-VLDL particle. Alternatively, apoB fails to be lipidated and is incorrectly folded and sorted to degradation. The formation of mature triglyceride-rich VLDL is dependent on the bulk addition of triglycerides derived from cytosolic lipid droplets (LDs). **B**, If AUP1 is overexpressed, more pre-VLDL particles are sorted to post-translational degradation. Likewise, accumulation of AUP1 on LDs may hamper apoB lipidation and VLDL assembly. Thus, fewer VLDL particles are formed. **C**, When AUP1 is decreased, fewer apoB-containing lipoproteins are sorted to post-translational degradation and more LDs are formed. Thus, more mature VLDL particles are secreted from the liver. Stars indicate AUP1. ER indicates endoplasmic reticulum.

References

1. Joseph JJ, Golden SH. Type 2 diabetes and cardiovascular disease: what next? *Curr Opin Endocrinol Diabetes Obes*. 2014;21:109–120. doi: 10.1097/MED.0000000000000044.
2. Taskinen MR, Borén J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis*. 2015;239:483–495. doi: 10.1016/j.atherosclerosis.2015.01.039.
3. Borén J, Taskinen MR, Olofsson SO, Levin M. Ectopic lipid storage and insulin resistance: a harmful relationship. *J Intern Med*. 2013;274:25–40. doi: 10.1111/joim.12071.
4. Adiels M, Taskinen MR, Packard C, Caslake MJ, Soro-Paavonen A, Westerbacka J, Vehkavaara S, Häkkinen A, Olofsson SO, Yki-Järvinen H, Borén J. Overproduction of large VLDL particles is driven by increased liver fat content in man. *Diabetologia*. 2006;49:755–765. doi: 10.1007/s00125-005-0125-z.
5. Olofsson SO, Borén J. Apolipoprotein B secretory regulation by degradation. *Arterioscler Thromb Vasc Biol*. 2012;32:1334–1338. doi: 10.1161/ATVBAHA.112.251116.
6. Araki K, Nagata K. Protein folding and quality control in the ER. *Cold Spring Harb Perspect Biol*. 2012;4:a015438. doi: 10.1101/cshperspect.a015438.
7. Klemm EJ, Spooner E, Ploegh HL. Dual role of ancient ubiquitous protein 1 (AUP1) in lipid droplet accumulation and endoplasmic reticulum (ER) protein quality control. *J Biol Chem*. 2011;286:37602–37614. doi: 10.1074/jbc.M111.284794.
8. Spandl J, Lohmann D, Kuerschner L, Moessinger C, Thiele C. Ancient ubiquitous protein 1 (AUP1) localizes to lipid droplets and binds the E2 ubiquitin conjugase G2 (Ube2g2) via its G2 binding region. *J Biol Chem*. 2011;286:5599–5606. doi: 10.1074/jbc.M110.190785.
9. Jo Y, Hartman IZ, DeBose-Boyd RA. Ancient ubiquitous protein-1 mediates sterol-induced ubiquitination of 3-hydroxy-3-methylglutaryl CoA reductase in lipid droplet-associated endoplasmic reticulum membranes. *Mol Biol Cell*. 2013;24:169–183. doi: 10.1091/mbc.E12-07-0564.
10. Zhang J, Zamani M, Thiele C, Taher J, Amir Alipour M, Yao Z, Adeli K. AUP1 (ancient ubiquitous protein 1) is a key determinant of hepatic very-low–density lipoprotein assembly and secretion. *Arterioscler Thromb Vasc Biol*. 2017;37:633–642. doi: 10.1161/ATVBAHA.117.309000.
11. Wiggins D, Gibbons GF. The lipolysis/esterification cycle of hepatic triacylglycerol. Its role in the secretion of very-low-density lipoprotein and its response to hormones and sulphonylureas. *Biochem J*. 1992;284(pt 2):457–462.
12. Salter AM, Wiggins D, Sessions VA, Gibbons GF. The intracellular triacylglycerol/fatty acid cycle: a comparison of its activity in hepatocytes which secrete exclusively apolipoprotein (apo) B100 very-low-density lipoprotein (VLDL) and in those which secrete predominantly apoB48 VLDL. *Biochem J*. 1998;332(pt 3):667–672.
13. Gibbons GF, Islam K, Pease RJ. Mobilisation of triacylglycerol stores. *Biochim Biophys Acta*. 2000;1483:37–57.
14. Rustaeus S, Lindberg K, Stillemark P, Claesson C, Asp L, Larsson T, Borén J, Olofsson SO. Assembly of very low density lipoprotein: a two-step process of apolipoprotein B core lipidation. *J Nutr*. 1999;129(suppl 2S):463S–466S.
15. Lee S, Zhang C, Kilicarslan M, et al. Integrated network analysis reveals an association between plasma mannose levels and insulin resistance. *Cell Metab*. 2016;24:172–184. doi: 10.1016/j.cmet.2016.05.026.
16. Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics. Tissue-based map of the human proteome. *Science*. 2015;347:1260419. doi: 10.1126/science.1260419.

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