Cardiovascular disease remains the leading cause of death around the world. 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. 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. It is therefore not surprising that VLDL secretion—and thus the concentration of plasma triglycerides—is highly dependent on the availability of hepatic lipids.

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. 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.

Interestingly, recent studies have shown that LDs are not only involved in lipid storage but are also important for proteasomal protein degradation and autophagy. The AUP1 (ancient ubiquitous protein 1) was identified as the first LD-associated protein involved in ER-associated degradation. The carboxyl terminus of AUP1 binds the E2 ubiquitin conjugases. 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.

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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


Key WORDS: Editorials ■ autophagy ■ cause of death ■ endoplasmic reticulum ■ lipid droplets ■ obesity
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