Glycomics & Lipidomics

Extended Abstract

Lipid efflux from liver

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Abstract

Secretion of lipids in the form of very low-density lipoproteins (VLDL) by the liver plays an important role in maintaining overall body lipid homeostasis. Any abnormality associated with this physiological process can lead to severe metabolic disorders such as hyperlipidemia, hepatic steatosis, etc. The rate-limiting step in the secretion of VLDLs from the liver is their transport from the endoplasmic reticulum (ER) to the Golgi and represents a potential therapeutic target in controlling VLDL secretion. We have identified a distinct ER-derived vesicle, VLDL transport vesicle (VTV), which facilitates the targeted delivery of VLDLs from the ER to the Golgi. To find out the factors that regulate the biogenesis of these vesicles, we performed detailed proteomic and biochemical analyses. Our data revealed that two small MR proteins, cideB and SVIP are present in VTV but not in other ER-derived vesicles. Our morphological and co-immunoprecipitation data revealed that both cideB and SVIP specifically interact with VLDL structural protein, apolipoproteinB100. To examine the roles of these proteins in VTV-biogenesis, we carried out an in vitro ER-budding assay. We showed that either blocking or knockdown of cideB and SVIP abrogates VTV-budding and VLDL secretion from hepatocytes. We conclude that cideB and SVIP control VLDL/ lipid secretion from the liver by regulating VTV-formation and their identification is critical for the development of novel therapeutics for dyslipidemia. Cholesterol efflux from lipid-loaded cells is a key athero-protective event that counteracts cholesterol uptake. The imbalance between cholesterol efflux and uptake determines the prevention or development of atherosclerosis. Many proteins and factors participate in the cholesterol efflux event. However, there are currently no systematic models of reverse cholesterol transport (RCT) that include most RCT-related factors and events. On the basis of recent research findings from other and our laboratories, we propose a novel model of one center and four systems with coupling transportation and networking regulation.

This model represents a common way of cholesterol efflux; however, the systems in the model consist of different proteins/factors in different cells. In this review, we evaluate the novel model in vascular smooth muscle cells (VSMCs) and macrophages, which are the most important original cells of foam cells. This novel model consists of 1) a caveolae transport center, 2) an intracellular trafficking system of the caveolin-1 complex, 3) a transmembrane transport system of the ABC-A1 complex, 4) a transmembrane transport system of the SR-B1 complex, and 5) an extracelluar trafficking system of HDL/Apo-A1. In brief, the caveolin-1 system transports cholesterol from intracellular compartments to caveolae. Subsequently, both ABC-A1 and SR-B1 complex systems transfer cholesterol from caveolae to extracellular HDL/Apo-A1. The four systems are linked by a regulatory network. This model provides a simple and concise way to understand the dynamic process of atherosclerosis. Plasma levels of high-density lipoproteins (HDL) and apolipoprotein A-I (apoA-I) are inversely correlated with the risk of cardiovascular disease. One major atheroprotective mechanism of HDL and apoA-I is their role in reverse cholesterol transport, i.e., the transport of excess cholesterol from foam cells to the liver for secretion. The ATP-binding cassette transporters ABCA1 and ABCG1 play a pivotal role in this process by effluxing lipids from foam cells to apoA-I and HDL, respectively. In the liver, ABCA1 activity is one rate-limiting step in the formation of HDL. In macrophages, ABCA1 and ABCG1 prevent the excessive accumulation of lipids and thereby protect the arteries from developing atherosclerotic lesions. However, the mechanisms by which ABCA1 and ABCG1 mediate lipid removal are still unclear.

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