Blood cholesterol transport: the assembly and secretion of apoB-containing lipoproteins.

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The major plasma lipoproteins- chylomicrons, VLDL, LDL, and HDL, can be broadly divided into those that contain apolipoprotein B (apoB) and those that do not. The apoB-containing lipoproteins are chylomicrons, VLDL, and LDL, and they are serve to transport dietary (chylomicrons) or hepatically synthesized (VLDL, LDL) lipids to peripheral cells. HDL, which contains apoAI, functions in reverse lipid transport- mainly the return of cholesterol from peripheral cells to the liver. Thus, apoB-lipoproteins are considered pro-atherogenic and HDL anti-atherogenic.

We have focused on the assembly and secretion of hepatic VLDL, which is the precursor of LDL. VLDL assembly is a complex process that involves the coordinated assembly of at least 4 lipid components and at least 3 proteins, including its major one, apoB. In the 70's and 80's it was discovered that without apoB no VLDL would form, and that the net amount of VLDL particles secreted by the liver was regulated at the level of apoB degradation. My lab has discovered or co-discovered 3 major processes that mediate apoB degradation, with each metabolically regulated by different factors. The first is ER-associated degradation, which occurs when lipid synthesis or transfer in the ER is deficient and which is mediated by the proteasome; the second is post-ER presecretory proteolysis, which is regulated by polyunsaturated fatty acids and is accomplished by autophagy; and the third is re-uptake from the cell surface, which is regulated by LDL receptor activity, so that apoB degradation in this case is mediated by lysosomes. These pathways will be reviewed, and new data about insulin-regulated apoB degradation will be presented. This process may be defective in insulin-resistant states, and may explain the high VLDL and low HDL plasma levels observed in patients with this disorder.

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