Mechanisms of Lipid Transport and Blood Lipid Levels

Biochemistry: A Short Course available in reserve[1].

[1] John L Tymockzko, Jeremy M Berg, and Lubert Stryer. *Biochemistry: A Short Course*. W.H. Freeman and Co, New York, NY, 3rd edition, 2015

Contents

Learning Objectives

- Explain why lipoproteins are necessary for triglyceride and cholesterol transport.
- Describe the main carriers of cholesterol and triglyceride throughout the body, including how their apolipoproteins affect their endocytosis or catabolism.
- Evaluate how different alleles of *APOE* can alter risk of cardiovascular and neurodegenerative diseases.
- Apply your knowledge of cholesterol transport to explain why someone may have changes in HDL and LDL levels.
- Understand the etiology of high cholesterol and its potential role in atherosclerosis.
- Apply your understanding of cholesterol absorption, synthesis and transport to evaluate the relationships between dietary cholesterol and triglycerides and cardiovascular risk.
- Explain the role of lipoprotein lipase in lipid transport, including how it is regulated.

Triglyceride and Fatty Acid Transport Mechanisms

Transportation of lipids presents some logistical problems. Since they are inherently insoluble, lipids need to be either solubilized prior to tranport to other tissues via the blood stream. This is accomplished in two ways. One is the packaging of triglycerides and cholesterol esters into lipoprotein particles, such as the chylomicrons discussed earlier this unit. The second mechanism is to break triglycerides down to fatty acids, where they can bind to solubilizing proteins called albumin within the blood.

Lipolysis and Fatty Acid Transport

Lipoprotein Particles in the Body

In terms of moving triglycerides and cholesterol esters, we have a variety of lipoprotein particles that play different roles in the body. These are summarized in Table 1. There are three main transport routes. The first is from the enterocyte to the periphery, mediated by chylomicrons. The second is from the liver to the periphery, mediated by VLDL. The third is from the periphery back to the liver, mediated by HDL/LDL. We will discuss each of these in the next few sections

Table 1: Summary of lipoprotein particles.

Particle	Source	Destination
Chylomicron	Enterocyte	Adipose, Muscle, Liver
VLDL	Liver	Adipose, Muscle
IDL	VLDL	Liver or LDL
HDL	Endothelial	LDL
LDL	IDL/HDL	Liver

Table 2: Apolipoprotein summary. Some key things to remember, ApoB48 is specifically made in the enterocyte. ApoB100 and ApoE the ligands for the LDL Receptor allowing for particle uptake. ApoCII is the coenzyme for

The Role of Chylomicrons and VLDL

The goal of these lipoprotein particles is to move lipids from the source[2] to peripheral tissues which might be better equiped to utilize or store lipids. As summarized in Table 2, these particles are characterized by the presence of Apolipoproteins E and CII.

[2] The enterocyte for chylomicrons for dietary lipids, or the liver for VLDL.

The Role and Regulation of Lipoprotein Lipase

Both VLDL and chylomicrons are targetted to peripheral tissues. This specificity is mediated by Apolipoprotein CII. This lipid acts as an activator of a triglyceride lipase known as *Lipoprotein Lipase* or LPL. This lipase resides on the lumen of blood vessels, adjacent to muscle and adipose tissues. Once activated by ApoCII binding, LPL breaks down the triglycerides in the particle and releases free fatty acids. These free fatty acids enter the cell where they can be stored (in the case of adipocytes), or used as fuel (in the case of muscle cells).

LPL HAS LONG KNOWN TO BE INACTIVATED BY DIETS HIGH IN SATURATED FATS. This meant that when saturated fat levels were increased, LPL activity was reduced. This is a negative feedback mechanism wherein intracellular lipids can signal to the LPL on the extracellular surface to prevent additional fat uptake. The molecular underpinnings of this phenomena have recently been determined and involves a protein called ANGPTL4[3]. ANGPTL4 is induced by elevated fatty acids levels in the cell, and is secreted where it binds to and inhibits LPL (more details about this can be found in the recent review by Dijk and Kersten [2014]). Mutations in either the *LPL* or *ANGPTL4* genes result either impaired, or enhanced blood lipid clearance respectively and as a result either increased or decreased risk of cardiovascular disease [Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators et al., 2016].

[3] Unhelpfully, an abbreviation for Angiopoietin-like 4.

DEPLETED VLDL ARE KNOWN AS IDL, WHERAS DEPLETED CHYLOMICRONS ARE KNOWN AS CHYLOMICRON REMNANTS. Once these lipoproteins have delivered their triglyceride content they are known as chylomicron remnants or intermediate[4] density lipoproteins. Due to the presence of ApoE on their surface these particles can be absorbed by the liver and the apolipoproteins and phospholipids reused.

[4] This indicates intermediate in density between VLDL and LDL

APOE VARIANTS ARE ASSOCIATED WITH DISEASE RISK. Since this apolipoprotein is present on both chylomicrons and VLDL then IDL. There are four variants of the *APOE* gene numbered 1-4. Of these

isoform ApoE2 is thought to be protective while ApoE4 is a risk factor for late-onset Alzheimer's disease [Poirier et al., 1993, Corder et al., 1993]. When fed a hyperlipidemic diet, individuals with the *APOE4* variants have much more dramatic increases in LDL than those with other genotypes [Lehtimäki et al., 1992]. This suggests that for those consuming diets rich in saturated fats, and with the *APOE4* there may be an exacerbated risk, although to our knowledge this has not been tested.

Reverse Cholesterol Transport

Cholesterol is primarily disposed of via bile salt generation and excretion, a process that occurs in the liver. Therefore cholesterol, which is made throughout the body is trafficked to the liver, a process known as *Reverse Cholesterol Transport*. This process is mediated by HDL and LDL particles.

Synthesis and Role of HDL

High density lipoprotein particles start off as nascent particles containing ApoAI, ApoAII and ApoB100 and very little cholesterol. As they pass through the circulation they bind cholesterol from the plasma membrane of tissues and become enriched with cholesterol. Eventually these HDL particles can be endocytosed in the liver where cholesterol can be disposed.

HDL transfers cholesteryl esters to and from the VLDL in exchange for phospholipids and triglycerides. This is done via cholesterylester transfer protein[5], and ensures that triglycerides are packaged in the LPL-accessible particles for peripheral transport, while excess cholesterol is delivered back to the liver for excretion. Inhibition of CETP results in an increase in the amount of HDL cholesterol in the bloodand was a heavily invested pharmacological area, but these drugs have shown limited cardiovascular benefits. The best thinking in this area is now that high HDL cholesterol is a marker of but not a cause of lowered cardiovascular risk.

[5] Abbreviated as CETP

LDL-mediated Transport to the Liver

Low density lipoproteins on the other hand are generated when IDL derived from VLDL remains in the circulation. These particles tend to be cholesterol rich, since the triglycerides have been taken up by the actions of LPL at peripheral tissues. These particles would normally be endocytosed by the liver, but this is dependent on the activity of the Low Density Lipoprotein Receptor, itself under control

of SREBP2. Recall that when intrahepatic cholesterol levels are high, SREBP2 is inactive, and LDLR is not produced. This means that when the liver has sufficient cholesterol[6] LDL particles remain in the circulation[7]. This is known as "bad" cholesterol because elevations are associated with cardiovascular disease.

[6] Potentially because of sufficient cholesterol synthetic activity.

[7] As a thought exercise, consider what would happen if you had a *LDLR* mutation, how would that affect cholesterol retrieval? How do you think it would affect cholesterol synthesis? This is the case for individuals with a disease known as familial hypercholesterolemia.

Cholesterol Export to Bile

Within the liver, bile salts are generated limited by the activity of 7-α-hydroxylase[8] and exported to the gall bladder for release into the digestive system. Separate from the SREBP2-dependent cholesterol regulatory system, the production of bile salts is sensed by the FXR sensing system.

[8] We discussed this in the lipid digestion lecture

Blood Lipids and Cardiovascular Risk

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