Lipid Transport and Blood Lipid Levels

Lipid transport is essential to both the efficient storage, and effective use of lipids. Due to their semi-or total insoluble nature, triglycerides, cholesterol and fatty acids present some specific technical problems in terms of transportation. These processes rely on both carrier proteins such as albumin as well as lipoprotein particles to safely move lipids from one tissue to another. Inefficient co-ordination of lipid transport can lead to elevated blood lipids, which are highly associated with cardiovascular disease, a major cause of death in modern society. For more details about lipid transport refer to Chapter 18 in Lippincott's Illustrated Reviews: Biochemistry, available in reserve[1].

[1] Denise Ferrier. *Lippincott Illustrated Reviews: Biochemistry*. LWW, 1496344499, 7th edition, 2017. ISBN 1496344499

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.
- 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

As we described in the unit about lipid oxidation, the majority of our triglyceride stores are in adipose tissue. The release of free fatty acids and glycerol from adipose tissue is a highly regulated process, activated by adrenaline and inhibited by insulin (for more details see Zechner et al. [2012] for a review). The transport of free fatty acids after release from adipose tissue is mediated by proteins called albumin, a very abundant protein produced by the liver. Due to their semi-solubility, fatty acids also require transport systems and fatty acid binding proteins (abbreviated as FABP) to move through membranes and through the cytoplasm.

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

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.

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

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

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 LPL, allowing for lipid extraction to peripheral tissues.

Particle	ApoA	ApoB	ApoC	ApoE
Chylomicron	AV	B48	CII/CIII	E
VLDL	AV	B100	CI/CII	E
IDL		B100		E
HDL	AI/AII	B100		E
LDL		B100		

The Role of Chylomicrons and VLDL

Both chylomicrons and VLDL function to move lipids to peripheral tissues, either from the gastrointestinal tract or the liver respectively. These particles transport primarily *neutral lipids* rather than free fatty acids. Their assembly is also dependent on the production of the apolipoproteins and the presence of phospholipids, especially phosphatidylcholine for their synthesis. If choline levels are limited, either due to less active variants in *PEMT* or reduced dietary intake, the liver will be less able to assemble VLDL. This can result in increased hepatic steatosis, potentially leading to non-alcoholic fatty liver disease.

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). The levels of LPL are inversely regulated in adipose and muscle tissue. For example, insulin promotes LPL transcription in adipose tissue*To promote lipid storage. This is accomplished by transcriptional and* but decreases LPL transcription in muscle [Spooner et al., 1979]. The inverse is true during fasting.

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. To separate blood lipids between reverse and forward transport processes, sometimes the ratio betwen ApoB and ApoAI is determined[5].

[5] Consider based on the data in Table 2 what this ratio is actually measuring. As a hint, a high ApoB100/ApoA1 ratio is indicitave of elevated cardiovascular risk.

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[6], 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.

[6] 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[7] LDL particles remain in the circulation[8]. This is known as "bad" cholesterol because elevations are associated with cardiovascular disease.

[7] Potentially because of sufficient cholesterol synthetic activity.

[8] 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[9] 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.

[9] We discussed this in the lipid digestion lecture

Blood Lipids and Cardiovascular Risk

If fat transport systems (VLDL and LDL) exceed the ability to store lipids, these lipids remain in the blood. Akin to the hyperglycemia associated with impaired glucose disposal, and excesive glucose production, hyperlipidemia is associated with cardiovascular disease. Since triglycerides can be metabolized into energy by most tissues, hypercholesterolemia in particular has been long associated with cardiovascular risk [Keys et al., 1963].

Since cholesterol may exist in several lipoprotein particles, a more prognostic indicator is the amount of cholesterol in HDL particles relative to the amount of cholesterol in LDL particles, with the latter being more pathogenic[10]. Several mechanisms for LDL's specific association with cardiovascular risk have been proposed, but one possibility is that excess LDL is absorbed in blood vessel walls, promoting both atherosclerosis[11] and increasing the risk of thrombosis[12].

[10] HDL cholesterol levels may indicate a surplus of cholesterol transport particles, wheras LDL cholesterol likely indicates a surplus of cholesterol that cannot be adsorbed by the liver.

[11] The lipid-based coating of arteries, narrowing them and reducing their vascular flexibility.

[12] The release of a blood clot, often by lysis and release of an atherosclerotic plaque. This blood clot could travel to the brain or heard where a stroke or heart attack may occur.

From a dietary standpoint, data from several US-based cohort studies demonstrated that diets lower in saturated fat intake are associated with both total and LDL cholesterol, and associated with that, reductions in cardiovascular disease [Anderson et al., 1987, Wang et al., 2016]. This has recently been challenged by a large-multi country study[13] which indicated that increased carbohydrates plays a key role, maybe moreso than saturated fats with respect to cardiovascular disease [Dehghan et al., 2017]. For this large multi-ethnic study, there is some debate about whether regional dietary differences are fully accounted for, or if this is more reflective of diet-disease risk in a more diverse dataset.

[13] This is known as the PURE study, which evaluated over 135 000 participants in 18 countries.

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