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.

Key Concepts and Vocabulary

- Lipoprotein particles including:
  - Chylomicrons
  - Very Low Density Lipoproteins (VLDL)
  - Low Density Lipoproteins (LDL)
  - High Density Lipoproteins (HDL)
- Apolipoproteins, especially ApoB40, ApoB100 and ApoCII
- Lipoprotein Lipase and its regulation
- Reverse Cholesterol Transport
- Trans-Intestinal Cholesterol Export (TICE)
- Fatty Acid Transport and Albumin

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 and 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 distinct lipoproteins.

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 in tissues expressing the LDL receptor (mainly the liver). ApoCII is a coenzyme for LPL, activating it and 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 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[3] but decreases LPL transcription in muscle [Spooner et al., 1979]. The inverse is true during fasting.

[3] To promote lipid storage. This is accomplished by both transcriptional and post-translational mechanisms, reviewed in Kersten [2014].

LPL IS INACTIVATED BY DIETS HIGH IN SATURATED FATS. This meant that when saturated fat levels are 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 (see Figure 1). The molecular underpinnings of this phenomena have recently been determined and involves the transcriptional activation of a protein called ANGPTL4[4]. ANGPTL4 is induced by elevated when fatty acids levels in the cell activate the transcription factor PPARα. ANGPTL4 is theb 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].

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

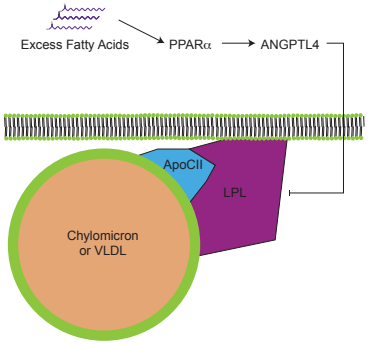

Figure 1: Regulation of Lipoprotein Lipase (LPL) by ANGPTL4.

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[5] 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.

[5] 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[6]. 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

[6] These are variants of the same gene, not different genes

et al., 1993].

Reverse Cholesterol Transport

Cholesterol is primarily disposed of via bile salt generation and excretion, a process that starts in the liver. Therefore cholesterol, which is made throughout the body is primarily trafficked to the liver, a process known as *Reverse Cholesterol Transport*. This process is mediated by both HDL and LDL particles. To separate blood lipids between reverse and forward transport processes, sometimes the ratio betwen ApoB and ApoAI is determined[7]. An alternate cholesterol disposal pathway is through the intestine, a process known as trans-intestinal cholesterol excretion[8]. In this pathway, cholesterol is transported by either HDL or LDL directly to the intestine for efflux. Estimates vary, but we think that somewhere between 20 and 40% of cholesterol excretion is through TICE, with the remainder through biliary transport [Temel and Brown, 2015].

[7] 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.

[8] TICE

Synthesis and Role of HDL

High density lipoprotein particles start off as nascent particles containing ApoAI, ApoAII and very little cholesterol. As they pass through the circulation they bind cholesterol from the plasma membrane of tissues and become enriched with cholesterol. Since most tissues make but cannot dispose of cholesterol, HDL is important for scavenging excess cholesterol from our cells. The HDL particles may be endocytosed in the liver where cholesterol can be disposed, but more often they transfer their cholesterol to LDL particles using an enzyme known as cholesterylester transfer protein[9]. This ensures that triglycerides are packaged in the LPL-accessible particles for peripheral transport, while excess cholesterol is delivered back to the liver or intestine 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 current thinking in this area is now that high HDL cholesterol is a marker of but not a cause of lowered cardiovascular risk.

[9] Abbreviated as CETP

LDL-mediated Transport to the Liver

Low density lipoproteins are generated when IDL derived from VLDL remains in the circulation, or when cholesterol is passed from an HDL to an LDL particle. 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 where there are LDL receptors. LDLR levels are under control of the SREBP2. Recall that when intrahepatic cholesterol levels are high, SREBP2 is inactive, and LDLR would not be produced. This means that when the liver has sufficient cholesterol, LDL particles remain in the circulation[10]. LDL cholesterol levels are correlated with coronary events. If one wants to understand the levels of LDL cholesterol in a person there are two measures. How much cholesterol is in the LDL fraction (LDL-C, should be less than 100 mg/dL) or how many LDL particles are present. Since each LDL contains one, and only one ApoB100 particle, and LDL particles vastly outnumber VLDL particles, if you determine the concentration of ApoB100 in blood, that is a measure of LDL particle number. Recent studies have suggested that it is this particle number, more so than the amount of cholesterol in the LDL fraction that is more predictive of cardiovascular events, though generally both incresae for most people [Cromwell et al., 2007, Mora et al., 2007].

[10] 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 salt synthesis is controlled by the activity of 7-α-hydroxylase[11] 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.

[11] We discussed this in the lipid digestion lecture

Blood Lipids and Cardiovascular Risk

If lipid 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[12]. 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[13] and increasing the risk of thrombosis[14].

[12] 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.

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

[14] 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[15] 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. In either case, both studies agree that more LDL cholesterol is generally associated with more heart disease.

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

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