# 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].

## 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 transport 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 in 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 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 equipped to utilize or store these lipids. As summarized in Table 2, these particles are characterized by distinct lipoproteins.

### 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 that is important for their synthesis. If choline levels are limited, either due to less active variants in *PEMT* or reduced choline 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.

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 source of chylomicrons transporting dietary lipids is the enterocyte, or the source of VLDL is the liver; the function of lipoproteins is to trasnport the lipids from both these sources, enterocyte and liver

Table 2: Apolipoprotein summary. Some key things to remember, ApoB48 is specifically made in the enterocyte. ApoB100 and ApoE are the ligands for the LDL Receptor allowing for LDL uptake in tissues expressing the LDL receptor (mainly the liver). ApoCII is a coenzyme for LPL thus 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 and Regulation of Lipoprotein Lipase

Both VLDL and chylomicrons are targeted 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 its free fatty acid content. These free fatty acids enter the cell where they can be stored (if they enter into the adipocytes), or are used as fuel (if they enter into the 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, where the muscle LPL trasncription is increased while that of the adipose tissue is reduced thus promoting muscle uptake of fat to be used as energy, while limiting adipose tissue ability to store this fat in times of energy need (fasting).

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

LPL ɪs ɪɴᴀᴄᴛɪᴠᴀᴛᴇᴅ ʙʏ ᴅɪᴇᴛs ʜɪɢʜ ɪɴ sᴀᴛᴜʀᴀᴛᴇᴅ ꜰᴀᴛs. This means that when saturated fat levels are increased, LPL activity is reduced. You can imagine how this is unbeneficial to the body, as the lipids in the blood cannot be taken up into the muscles or adipose tissue, therefore remaining in the blood and circulation. 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 involve the transcriptional activation of a protein called ANGPTL4[4]. ANGPTL4 is induced when excess fatty acid levels in the cell activate the transcription factor PPARα. ANGPTL4 is then secreted where it binds to and inhibits the activity of 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 in either impaired, or enhanced blood lipid clearance, respectively and as a result either lead to an 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.
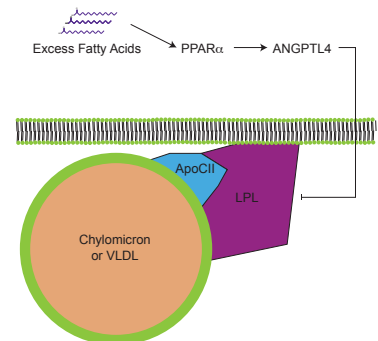


Figure 1: Regulation of Lipoprotein Lipase (LPL) by ANGPTL4.

Dᴇᴘʟᴇᴛᴇᴅ VLDL ᴀʀᴇ ᴋɴᴏᴡɴ ᴀs IDL, ᴡʜᴇʀᴇᴀs ᴅᴇᴘʟᴇᴛᴇᴅ ᴄʜʏ-ʟᴏᴍɪᴄʀᴏɴs ᴀʀᴇ ᴋɴᴏᴡɴ ᴀs ᴄʜʏʟᴏᴍɪᴄʀᴏɴ ʀᴇᴍɴᴀɴᴛs. Once these lipoproteins have delivered their triglyceride content into cells, they are either known as chylomicron remnants or intermediate[5] density lipoproteins (IDL). Due to the presence of ApoE on their surface, chylomicron remnants and IDL particles can be absorbed by the liver

[5] This indicates that this lipoprotein has intermediate density that falls in between VLDL and LDL's density

where the apolipoproteins and phospholipids can be reused.

*APOE* variants are associated with disease risk since this apolipoprotein is present on both chylomicrons and VLDL that then form IDL . There are four variants of the *APOE* gene numbered 1-4[6]. Of these isoforms, ApoE2 is thought to be protective while ApoE4 is considered a risk factor for late-onset Alzheimer's disease [Poirier et al., 1993, Corder 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 being through biliary transport [Temel and Brown, 2015].

## 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 most 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 to be used by peripheral tissues, 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 blood and thus CEPT inhibition was a heavily invested pharmacological area, but these drugs have shown limited cardiovascular benefits. The current thinking in this area is that high HDL cholesterol is a marker of lowered cardiovascular risk but does not cause

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

[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

[9] Abbreviated as CETP

lowered cardiovascular risk by itself.

## 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 IDL particle. These particles tend to be cholesterol rich, since the triglycerides have been already taken up due to the actions of LPL at peripheral tissues. These particles would normally be endocytosed by the liver where LDL receptors are found. LDLR levels are under control of the SREBP2. Recall that when intrahepatic cholesterol levels are high, SREBP2 is inactive, and thus 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 to consider. By looking at how much cholesterol is in the LDL fraction (LDL-C, should be less than 100 mg/dL) or how many LDL particles are present in the blood. Since each LDL contains one, and only one ApoB100 particle, and since LDL particles vastly outnumber VLDL particles, then if you determine the concentration of ApoB100 in blood, then 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 the cholesterol content in LDL and the LDL particle number incresae for most people simultaneously [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-$\alpha$-hydroxylase[11] and exported to the gallbladder 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[12].

[11] We discussed this in the lipid digestion lecture

[12] FXR is a bile acid sensor expressed in entero-hepatic tissues.

## Blood Lipids and Cardiovascular Risk

If lipid transport systems (of VLDL and LDL) have exceeded their ability to store lipids, then VLDL and LDL lipids remain in the blood. Akin to the hyperglycemia associated with impaired glucose disposal, and excessive glucose production, hyperlipidemia is associated with cardiovascular disease due to impaired lipid disposal. Since triglycerides can be metabolized into energy by most tissues, but

cholesterol cannot, 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 of cardiovascular risk is the amount of cholesterol in HDL particles relative to the amount of cholesterol in LDL particles, with the latter being more pathogenic[13]. 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[14] and increasing the risk of thrombosis[15].

FROM A DIETARY STANDPOINT, data from several US-based cohort studies demonstrated that diets lower in saturated fat intake are positively associated with both total and LDL cholesterol, and therefore associated with reductions in cardiovascular disease [Anderson et al., 1987, Wang et al., 2016]. This has recently been challenged by a large-multi country study[16] which indicated that increased carbohydrate intake plays a key role, maybe more so 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 increased heart disease risk.

[13] HDL cholesterol levels may indicate a surplus of cholesterol transport particles, whereas LDL cholesterol likely indicates a surplus of cholesterol that cannot be absorbed by the liver.

[14] The lipid-based coating of arteries, causing arteries to become narrower and reducing their vascular flexibility.

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

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

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