Blood Lipoprotein Production and Regulation

You should be aware of the importance of blood lipids to cardiovascular health. For individuals with poor nutrition and/or minimal to no regular exercise, there is an increased risk for elevations in blood lipids, including cholesterol and triacylglycerols. Abnormally elevated concentrations of total cholesterol, low density lipoproteins and triacylglycerols are all independent risk factors for atherosclerotic cardiovascular disease, including heat disease, peripheral vascular disease and stroke. Blood lipid abnormalities are also prevalent in individuals with diabetes. Given that exercise is a routine therapy to prevent and treat these conditions, it is logical that exercise physiologists learn about the synthesis and catabolism of these lipoprotein molecules.

The place to begin this tale is actually the digestive tract (Figure 1). Fats ingested in foods and liquids are mechanically and chemically degraded within the stomach and small intestine into component parts such as glycerol and fatty acids from triacylglyerols. **Cholesterol** is absorbed intact into the intestinal mucosa. The glycerol and fatty acids are combined to re-form triacylglycerols in the intestinal mucosa, and each of cholesterol, triacylglycerols and proteins are packaged into predominantly fat comprised lipoprotein molecules called **chylomicrons** (Figure 2).

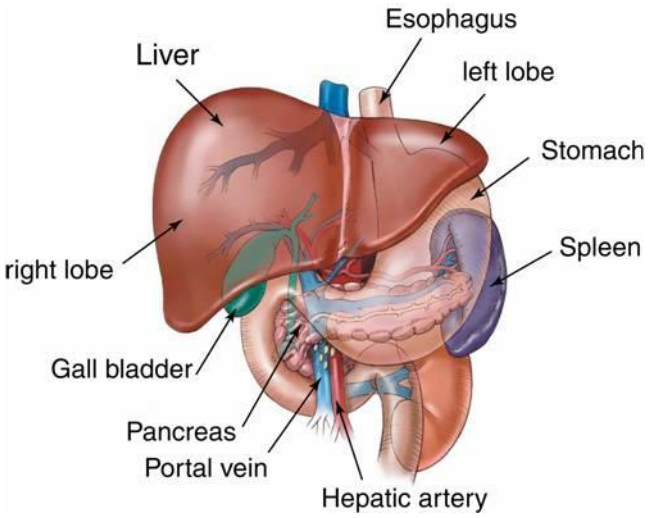

Figure 1. The intake of fats, including cholesterol, leads to the formation of chylomicrons that transport ingested fats to peripheral tissues and the liver.

Chylomicorons circulate in the blood and lymph to peripheral tissues, as well as to the liver. Within the blood, added proteins that can bind to specific types of lipoproteins or lipid molecules, called **apo-proteins**, can produce other types of lipoprotein conglomerates. Researchers can separate these lipoproteins based on their density (Table 1), and the proportional content of the lipoproteins for lipids and proteins have been determined.

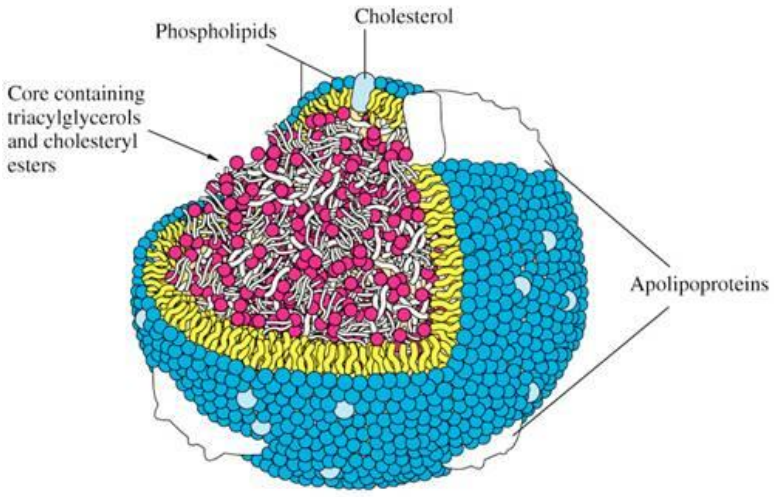

Figure 2. Illustration of a blood lipoprotein, along with the major constituents.

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The liver is also responsible for packaging lipids and proteins into lipoproteins. For example, the excess carbohydrate, fat and protein ingested in the diet are processed in the liver and converted to triacylglycerols and cholesterol (also synthesized from acetyl CoA). Originally, the triacylglycerols, cholesterol and specific apoproteins are packaged to form **very low density lipoprotein (VLDL)**.

Table 1. The lipoproteins found in the circulation, and their distinguishing characteristics.

Lipoprotein	Abbr'n	Density (g/mL)	Triacyl.	Chol.	Phos.	Pro.
Chylomicrons		**<1.006**	**85**	**4**	**9**	2
Very low density lipoproteins	**VLDL**	**0.95-1.006**	**50**	**19**	**18**	10
Low density lipoproteins	**LDL**	**1.006-1.063**	**10**	**45**	**20**	23
High density lipoproteins	HDL	1.063-1.210	4	17	24	55

The apolipoproteins are extremely important for understanding lipoproteins and their roles in metabolism and risk for the development of atherosclerotic cardiovascular disease. In essence, the apolipoproteins can be viewed as regulators of specific enzymes found along the lumen of blood vessel walls, or on the outer surface of the cells from specific tissues. Table 2 details the types of apolipoproteins, their presence on specific lipoproteins, and their functions.

Table 2. The apolipoproteins found on specific lipoproteins, and their functions.

Apolipoprotein	Lipoproteins	Functions
ApoA-I	**HDL**	Activates LCAT
ApoA-II	**HDL**	
ApoA-IV	**Chylomicrons, HDL**	
ApoB-48	**Chylomicrons**	
ApoB-100	**VLDL, LDL**	Binds to LDL receptors
ApoC-I	**VLDL, HDL**	
ApoC-II	**Chylomicrons, VLDL, HDL**	Activates lipoprotein lipase
ApoC-III	**Chylomicrons, VLDL, HDL**	Inhibits lipoprotein lipase
ApoD	**HDL**	
ApoE	**Chylomicrons, VLDL, HDL**	Initiates the removal of VLDL and chylomicron remnants

LCAT=lecithin-cholesterol acyl transferase

The process of transformation between the lipoprotein types is explained next. However, remember that the apoproteins found on the lipoproteins are important for their classification and functions, and to a large extent, these are initially determined by the liver, and then modified within the circulation.

Once the VLDLs leave the liver, they circulate to adipose tissue and muscle where **apoC-II** activates the enzyme lipoprotein lipase causing lipolyisis of the VLDL triacylglyerols, releasing **free fatty acids** (now labeled "free" as they are released [de-esterified] from the triacylglycerol) and glycerol. During rest conditions, adipose and muscle tissues resynthesize triacylglycerols for storage in lipid droplets. Figure 3 is a light microscope image of a collection of adipocytes, with the lipid droplet seen to take up most of the volume of the cell. Similar lipid droplets are found in skeletal muscle, but

of course, they are not as big and are of the size to fit between myofibrils and mitochondria.

The removal of triacylglycerols from the VLDL lipoprotein transforms it to a **low density lipoprotein (LDL)**, as it now contains a higher proportion of cholesterols, with most cholesterols being **cholesterol esters** (cholesterol with a fatty acid side chain addition to the terminal hydroxyl group). The function of the LDLs is to transport cholesterol to tissues, including the liver, that have surface protein receptors that complement or recognize **apoB-100**. These receptors are called **LDL-receptors** and facilitate the uptake of cholesterol and cholesterol esters into these cells. Remember that cholesterol is an extremely important component of cell membranes, and is essential for life. Cells need a constant supply of cholesterol, which can be met by the synthesis of cholesterol within the cell and also from within the liver. Of course, depending on dietary intake, there can also be appreciable cholesterol intake.

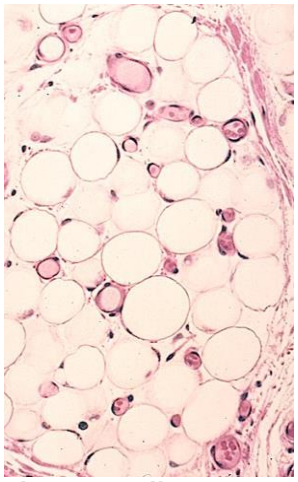

Figure 3. Adipocytes, as seen under moderate magnification with a light microscope.

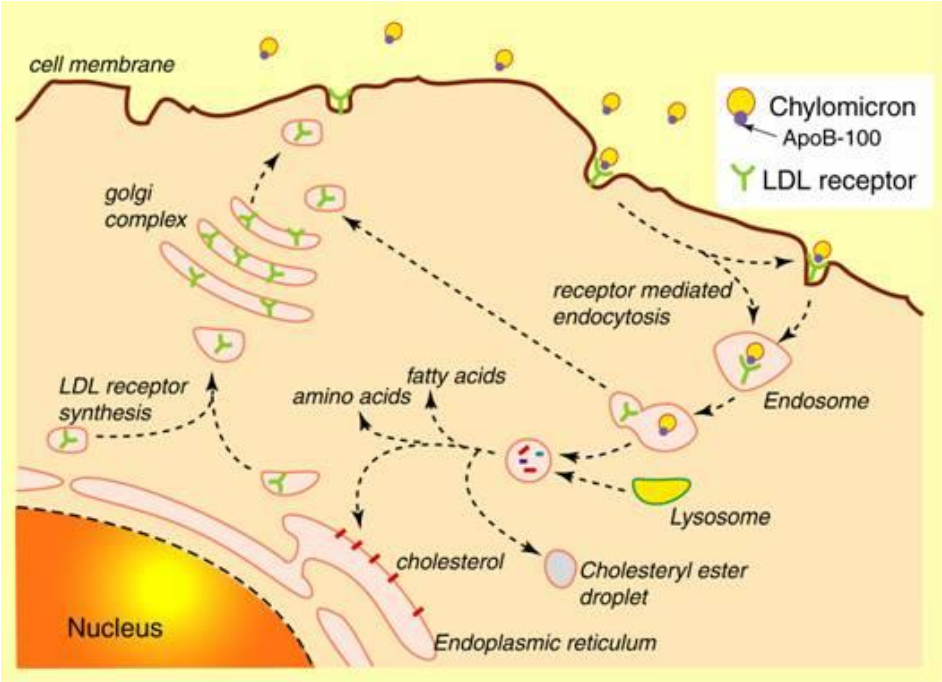

Figure 4. The process of endocytosis involving the LDL receptor and circulating LDL.

The binding of the LDL lipoprotein to the LDL receptor initiates the process of **endocytosis** (Figure 4), where the entire LDL is moved into the cell packaged in an **endosome** that contains enzymes specific the LDL degradation. Subsequently, the apoproteins are removed and catabolized to amino acids, triacylglycerols are de-esterified to free fatty acids, and cholesterols are released to fuse with inner

membranes or stored within lipid droplets. The LDL receptor proteins are retrieved and recycled back to the cell surface. In a normally functioning cell, increased cellular cholesterol induces **negative feedback** to the translocation of the LDL receptor back to the cell membrane, as well as inhibiting cell cholesterol synthesis via inhibition of the enzyme **HMG-CoA reductase**. In individuals that have faulty cellular regulation of cholesterol, cells continue to produce cholesterol despite normal or high blood lipoprotein cholesterol provision, decreasing the density of LDL receptors on the cell membrane, which in turn increases blood LDL concentrations. The inability to remove cholesterol from LDLs causes cholesterol release into the blood, where it accumulates forming plaque deposits and the development of atherosclerotic cardiovascular disease. This disease process remains the number 1 killer of humans in most developed countries.

Now let's get back to the remaining **HDL lipoprotein**. HDLs are produced in the liver, and originally are released into the circulation as small, protein rich particles, with minimal cholesterol and no cholesterol esters. The HDLs contain numerous apolipoproteins (Figure 2), and most importantly contain the enzyme **lecithin-cholesterol acyl transferase (LCAT)**. LCAT catalyzes the esterification of cholesterol to a cholesterol ester (Figure 5, Equation 1), which makes the cholesterol easier to transport in lipoproteins and store within cells. As more and more cholesterol is retrieved from the circulation as well as other lipoproteins (VLDLs and LDLs), the HDLs increase in size and return to the liver where the HDLs are incorporated into the liver by endocytosis, the cholesterol esters are removed and converted to bile salts and also down-regulate liver cholesterol synthesis. The HDL particles are recycled for release back into the circulation. Based on this function, it is correct to view HDLs as cholesterol scavenger lipoproteins, where they function to help clean the cardiovascular system of excess cholesterol. This is why high blood HDLs are a negative risk factor (decrease risk) for atherosclerotic cardiovascular disease.

$$Phosphatidylcholine\ (lecithin) + Cholesterol \xrightarrow{LCAT} Lysolecithin + Cholesterol\ ester$$

Equation 1

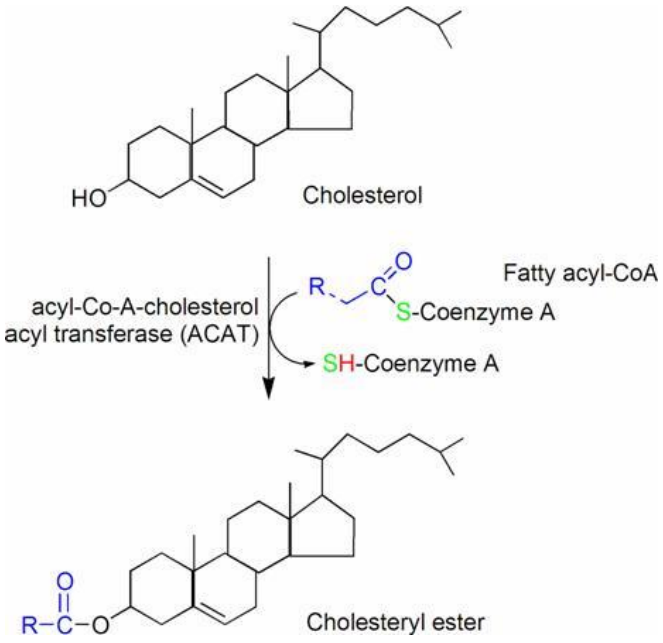

Figure 5. The chemical conversion of cholesterol to a cholesterol ester.

Glossary Words

cholesterol is a steroid alcohol (sterol) found in the cell membranes of all animal tissues, and which is transported to tissues within lipoprotein molecules in blood plasma.

chylomicrons are large lipoprotein molecules formed by the absorptive cells of the small intestine. Chylomicrons function to transport dietary lipids to the liver, adipose, cardiac and skeletal muscle tissues.

apo-proteins (apolipoproteins) are lipid-binding proteins present in chylomicrons, which function to influence one or more features of lipid transport in the blood depending on the specific type of apo-protein.

very low density lipoprotein (VLDL) is a type of lipoprotein formed in the liver from cholesterol and apo-lipoproteins. VLDLs are converted to LDLs in the blood.

apoC-II is a type of apo-protein that activates the enzyme lipoprotein lipase causing lipolysis of the VLDL triacylglyerols.

free fatty acids are the fatty acids released from the triacylglycerol during lipolysis.

low density lipoprotein (LDL) is a blood lipoprotein that transports cholesterol and triacylglycerols from the liver to the peripheral tissues.

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cholesterol esters are cholesterol molecules modified by the addition of an ester bond to an additional chemical compound, such as a fatty acid molecule.

apoB-100 is a type of apolipoprotein that is ofund on LDLs and is recognized by the LDL receptors of the liver.

LDL-receptors are cell membrane receptors to low density lipoproteins.

endocytosis is the molecular transport process where molecules bind to a membrane, and are then engulfed by the membrane and re-located in to the cell.

endosome is the membrane structure that engulfs a bound molecule during the process of endocytosis.

negative feedback is the process of cell or systemic regulation where the response to a stimulus decreases the magnitude of the original stimulus.

HMG-CoA reductase is the regulated enzyme responsible for cholesterol synthesis.

HDL lipoprotein is a high density lipoprotein, responsible for returning excess cholesterol from peripheral blood vessels to the liver.

Lecithin-cholesterol acyl transferase (LCAT) is the enzyme found on HDLs that catalyzes the esterification of cholesterol to cholesterol esters.