PCSK9 Inhibitors – Lipid Control

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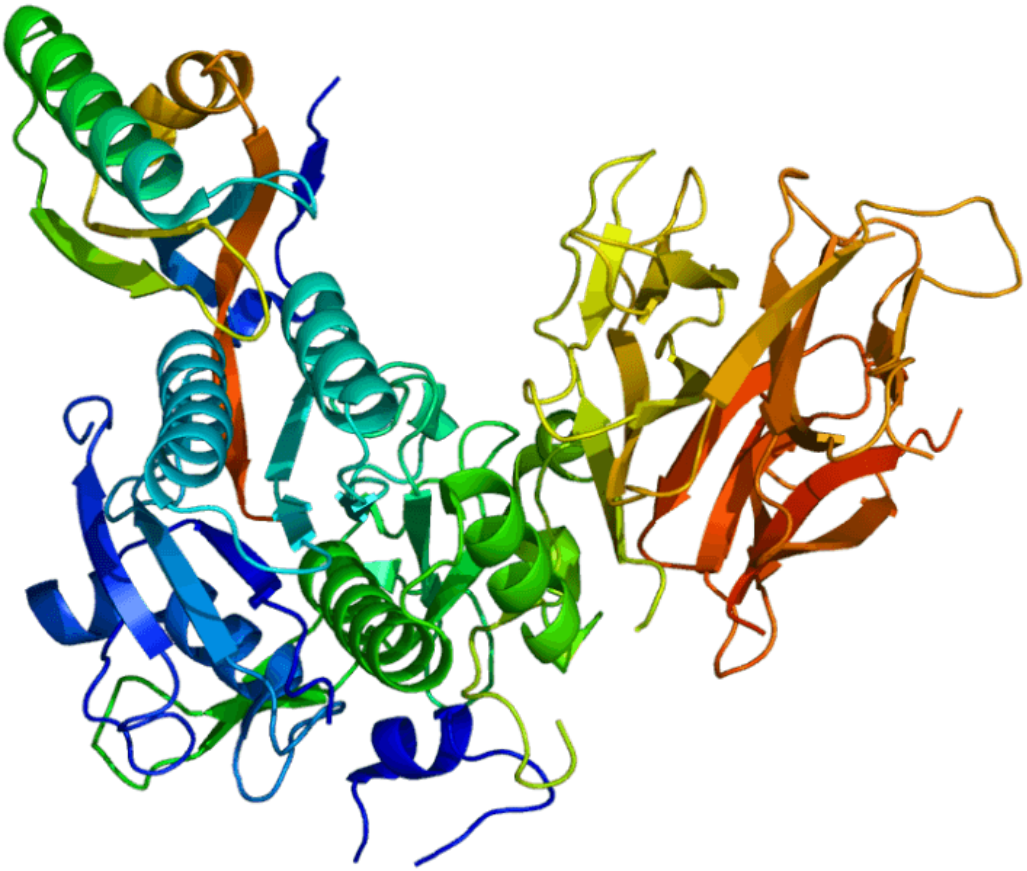
Science has taught us that fats and cholesterols, despite their negative connotation, play a significant role in keeping ourselves in tiptop shape. From structural purposes to that of hormone production, lipids are an essential part of our body's efforts to maintain homeostasis. However, problems do occur if there is an imbalance in the way that lipids are controlled by our system; this is where disorders such as the dyslipidemias come in. Fortunately, treatment modalities are also available to address this issue. In this case, it is important for us to understand the physiology of how our body maintains a healthy amount of lipids in order for us to gain some insight on how we approach patients with excessive lipid levels.



Lipid Transport

Overview of Lipoproteins

As you may have known by now, triglycerides and other forms of lipids are nonpolar in

nature. This means that by themselves, they would have some difficulty in traveling along with the polar intravascular and interstitial spaces; this is where **lipoproteins** come in.

Lipoproteins act as **shuttles that contain triglycerides and cholesterols**. They are essentially made up of a hydrophobic core composed of triglycerides and cholesterol esters, and a hydrophilic shell that contains apolipoproteins, phospholipids, and unesterified cholesterol molecules.

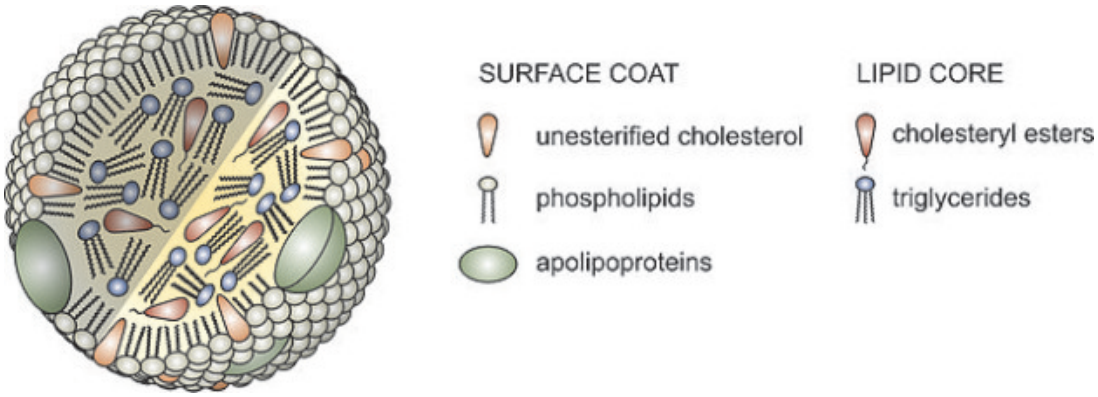


Image: "Lipoprotein particles are composed of a lipid core containing cholesteryl esters and triglycerides, and a surface coat of phospholipids, unesterified cholesterol, and apolipoproteins." by AntiSense. License: CC BY-SA 3.0

Lipoproteins take a variety of forms when functioning inside our body. Their classification actually depends on the proportions of their compositions.

Classification of Lipoproteins

Chylomicrons: Lipoproteins belonging to this group are the largest among all the lipoproteins and this is due to the number of triglycerides they contain. Chylomicrons carry exogenous (dietary) fats coming from the intestines into the liver via the lymph and the bloodstream.

Very-low-density lipoproteins (VLDL): VLDL are synthesized in the liver and carry triglycerides from there to the peripheries. There, the lipids are either metabolized for fuel or stored as adipose tissues. VLDL is second to chylomicrons when it comes to density and size.

Low-density lipoproteins (LDL): These lipoproteins come into being once a certain amount of triglycerides are taken out of VLDL. Cholesterols in the body, along with other lipids, are primarily carried by LDL. This lipoprotein is a significant indicator of hypercholesterolemia and is therefore usually screened in routine workups.

High-density lipoproteins (HDL): Unlike the rest of the lipoproteins, HDL actually carries lipids in a reverse route. Instead of delivering triglycerides and cholesterols to the peripheries, they somewhat 'clean up' the peripheries from excess lipids and carry them back to the liver for metabolism or excretion.

Lipoprotein Metabolism

Synthesis of Lipoproteins

Lipoproteins vary in the way that they are synthesized in the body. For instance, chylomicrons are synthesized in the endoplasmic reticulum of the absorptive cells lining

the intestines, while VLDL are secreted from the hepatocytes. Although they have different places of origin and directions of lipid delivery, they actually have similar compositions, functions, and process of formation.

As mentioned earlier, LDL are products of the triglyceride depletion of VLDL. This explains how some treatments directed solely to address hypertriglyceridemia cause a 'beta shift' phenomenon where, in an increase in the plasma, LDL follows after a decrease in triglyceride levels in the body. Aside from this, VLDL degradation also produces **VLDL remnants (IDL)** which are taken up by hepatocytes, ready for metabolism and excretion.

HDL derive their apoprotein content from the liver and the intestines. As for their hydrophobic core, HDL forms it by getting lipids from the surface monolayers of VLDL and chylomicrons while lipolysis is going on. HDL also get a significant amount of lipids, especially cholesterol from those lying around the peripheries and carry them back to the liver. The transfer of cholesterol to hepatic receptor cells, in exchange for substances needed for HDL structure maintenance, can occur in a direct or indirect method, the first involving endocytosis.

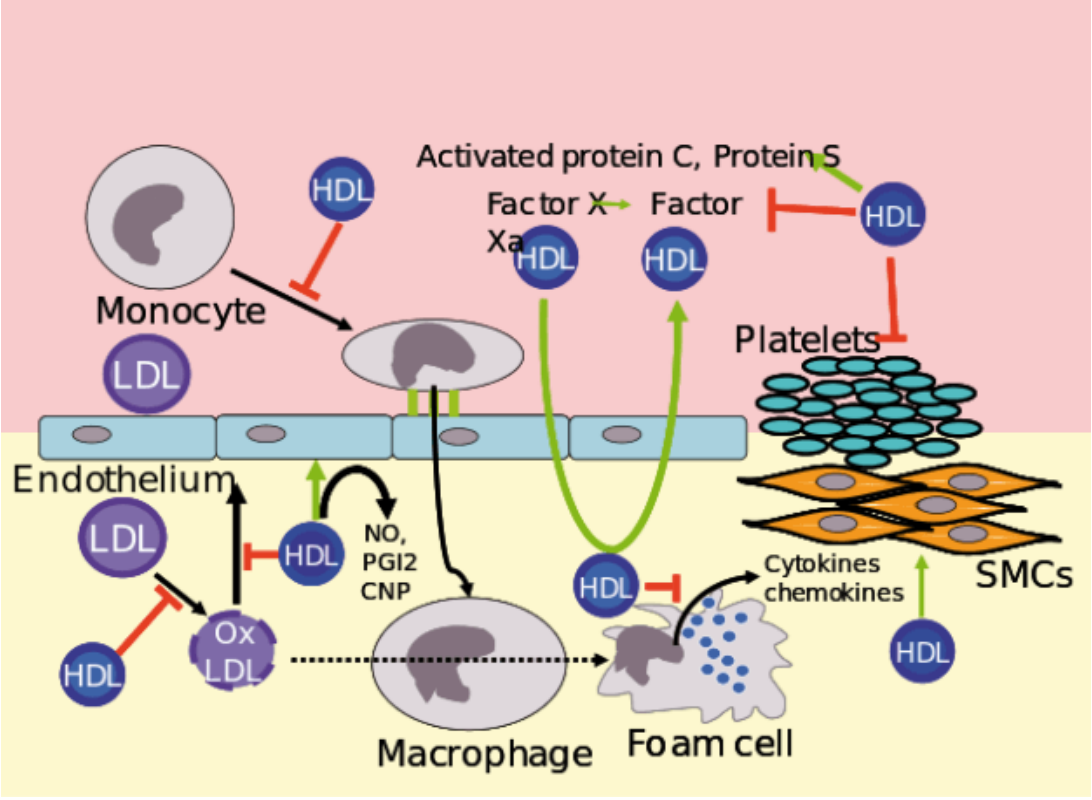


Image: "HDL" by Rfch. License: Public Domain

Degradation of Lipoproteins

Chylomicrons and VLDL

In under an hour, chylomicrons and VLDL can easily be eliminated from the bloodstream. This is made possible with the help of **lipoprotein lipase** or **LPL.** This enzyme is found in various locations in the body, including the walls of the blood capillaries, the heart, liver sinusoids, lungs, and spleen, among many others. However, the most active of these are the ones found in the endothelium of capillaries. LPL in the liver is also responsible for the

degradation of chylomicron remnants and HDL.

Hydrolysis is the main feature or LPL. It hydrolyzes lipoproteins in the presence of cofactors, such as **phospholipids** and **apo C-II.** Once triglycerides are liberated from this process, it is further hydrolyzed into free fatty acids and glycerols which can either go to storage in adipose cells or for use in tissues that require ketone for energy, such as the heart. The location of the LPL also dictates the predisposition of fatty acids to metabolism or storage. For example, LPL found in the heart has a high affinity for triglycerides which explains why fatty acids from triglyceride metabolism, during starvation, are redirected to the heart.

LDL

LDL, on the other hand, is metabolized in cells containing an **LDL receptor**. This receptor is specific for LDL as it detects **apo B-100,** an apoprotein unique to this lipoprotein. The majority of this degradation occurs in the liver, while a certain degree occurs in extrahepatic tissues.

LDL receptors, however, do not exist indefinitely. After functioning for some time, they are eventually degraded by proteins. One of these includes the enzyme **proprotein convertase subtilisin/kexin type-9** or **PCSK9**. PCSK9 works by binding to the LDL receptor, causing the receptor to undergo a series of changes leading to an eventual degradation. Without these receptors, cells capable of metabolizing LDL would not be able to do such.

HDL

HDL is metabolized by the help of **class B receptor B1 (SR-B1)** in the liver and other extrahepatic tissues that might use the cholesterol contained in the lipoproteins for hormone synthesis. SR-B1 receptors have high affinity to **apo A-I**, the distinct apoprotein found in HDL. Once SR-B1 bind to HDL, these empty the lipoprotein of its contained cholesterol and use it for steroidogenesis, or excrete it as bile salts.

Disorders Affecting Lipid Metabolism

Dyslipidemias

This group of disorders could be categorized into either **primary or secondary**.

Primary dyslipidemia is the ones that are usually not associated with external causes and may be brought about by single-gene mutations that could alter lipoprotein synthesis or degradation. Examples are listed on the table below:

Genetic disorder	Gene defect	Elevated lipoproteins	Transmission
Hypertriglyceridemia			
Lipoprotein lipase deficiency	LPL	Chylomicrons, VLDL	Autosomal recessive
Familial apoC-II deficiency	APOC2	Chylomicrons, VLDL	Autosomal recessive
ApoA-V deficiency	APOA5	Chylomicrons, VLDL	Autosomal recessive
GPIHBP1 deficiency	GPIHBP1	Chylomicrons	Autosomal recessive
Combined Hyperlipidemia			

Familial hepatic lipase deficiency	LIPC	VLDL remnants, HDL	Autosomal recessive
Familial dysbetalipoproteinemia	APOE	Chylomicron remnants, VLDL remnants	Autosomal recessive
Hypercholesterolemia			
Familial hypercholesterolemia	LDLR	LDL	Autosomal dominant
Familial defective apoB-100	APOB	LDL	Autosomal dominant
Autosomal dominant hypercholesterolemia, type 3	PCSK9	LDL	Autosomal dominant
Autosomal recessive hypercholesterolemia	LDLRAP	LDL	Autosomal recessive
Sitosterolemia	ABCG5 or ABCG8	LDL	Autosomal recessive

(Table adapted from Harrison's Principles of Internal Medicine, 19th ed. by Fauci AS, et al.)

Secondary dyslipidemias, on the other hand, are manifested as **imbalances in the plasma levels of triglycerides and lipoproteins** as a result of poor diet, co-existing diseases or concurrent intake of other medications. Other more specific examples of causes may include:

- High-carbohydrate diet
- Excessive alcohol intake
- Obesity and insulin resistance
- Excessive glucocorticoid levels

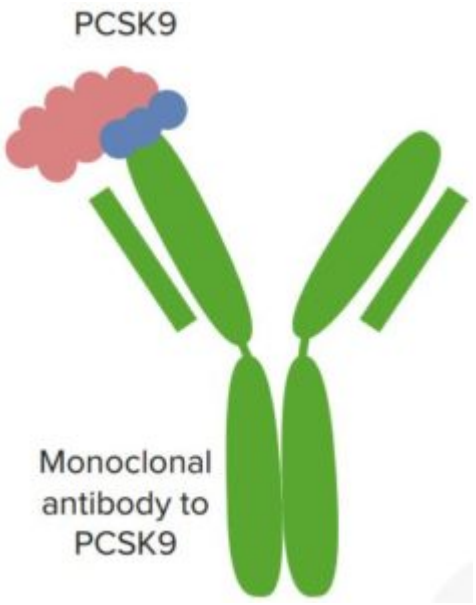
Treatment

The goal of treatment for patients having dyslipidemia is usually directed towards the prevention of more serious diseases such as cardiovascular events and pancreatitis. In order to reach and maintain this, lifestyle modifications and thorough meal planning are instituted early in the diagnosis. More often than not, patients are also prescribed with pharmacologic modalities that are designed to suit the type of dyslipidemia and the concurrent risks that they have.

PSCK9 Inhibitors

- **Alirocumab**
- **Evolucumab**
- **Bococizumab**

Mechanism of action

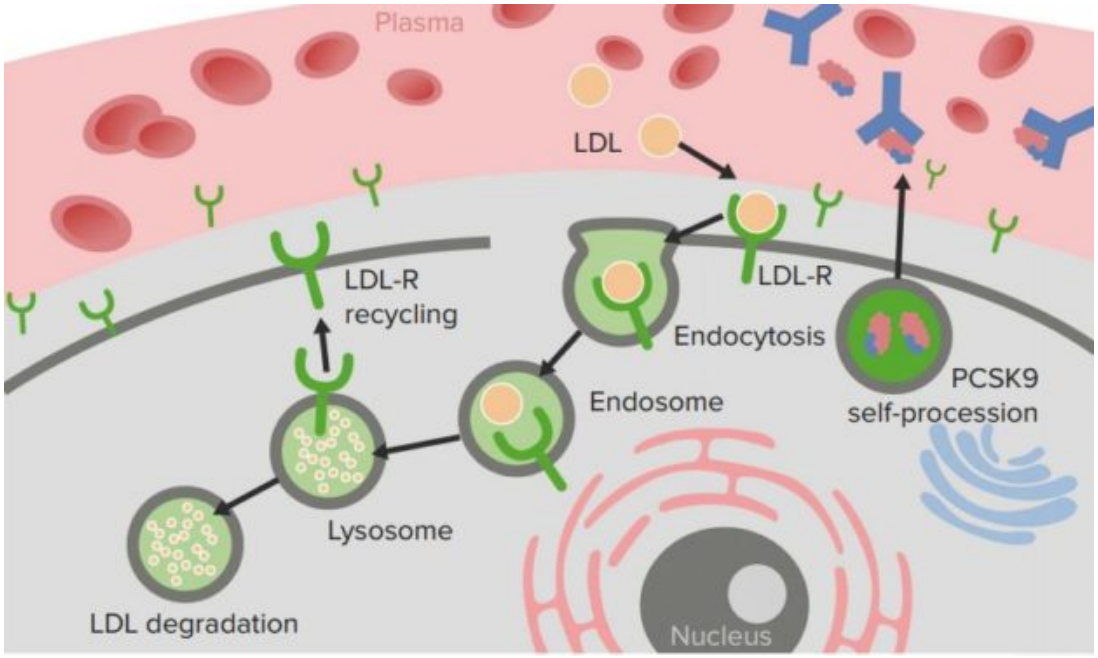


: “PCSK9 Inhibitors” Image created by Lecturio

The relatively new **PSCK9 inhibitors** are essentially **monoclonal antibodies** designed to ultimately reduce the circulating levels of LDL in the plasma. These inhibitors work by binding to free-floating PCSK9 in the bloodstream, keeping them binding to active LDL receptors in the liver and in extrahepatic tissues, and degrading them.

With this mechanism, cellular endocytosis of LDL is continued and LDL receptors are continually recycled for use. When taken with HMG CoA reductase inhibitors which are medications designed to inhibit cholesterol synthesis, PCSK9 inhibitors can be very effective in controlling the lipid levels of patients with problems in lipid metabolism. This drug is given subcutaneously once or twice a month.

PCSK9 inhibitors are eliminated in the body by either of two ways: by the linear, **non-specific clearance pathway** in the reticuloendothelial system, or by a **nonlinear, saturable clearance pathway**. Since this medication is made up of antibodies which constitute a relatively large structure, it cannot pass through the renal tubules and are subsequently not eliminated through the kidneys.



"PCSK9 Inhibitors. Mechanism of action" Image created by Lecturio

These medications have only been FDA-approved in the year 2015. More research is underway to measure their effectiveness in controlling dyslipidemias, and their efficiency in decreasing the patients' risk for complications such as cerebrovascular accidents and ischemic heart disease.

Indications

Usually, patients having trouble **controlling their cholesterol and LDL levels** for a variety of reasons are first prescribed with HMG CoA reductase inhibitors or statins. Although a lot of patients demonstrate therapeutic drops in their plasma lipid levels, this may not be true to all. Others also report some side effects associated in taking this drug. For this reason, PCSK 9 inhibitors are developed in order to be prospectively prescribed alone, or with statins, and to reduce the required dosage of the latter. In fact, there have already been clinical trials proving that **lipid control is more efficient** when statins are taken with PCSK9 inhibitors, than when statins are taken alone.

Side Effects and Precautions

Since PCSK9 inhibitors are essentially made up of monoclonal antibodies, the possibility of **allergic reactions** should be anticipated in susceptible individuals. Although generally well-tolerated by most of the subjects in clinical trials, some patients have reported minor signs and symptoms experienced while taking the medication. These include soreness at the injection site, itching, nasopharyngitis, joint pain, neurocognitive manifestations, and flu-like symptoms.

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Notes