5.2.4

Lipoproteins

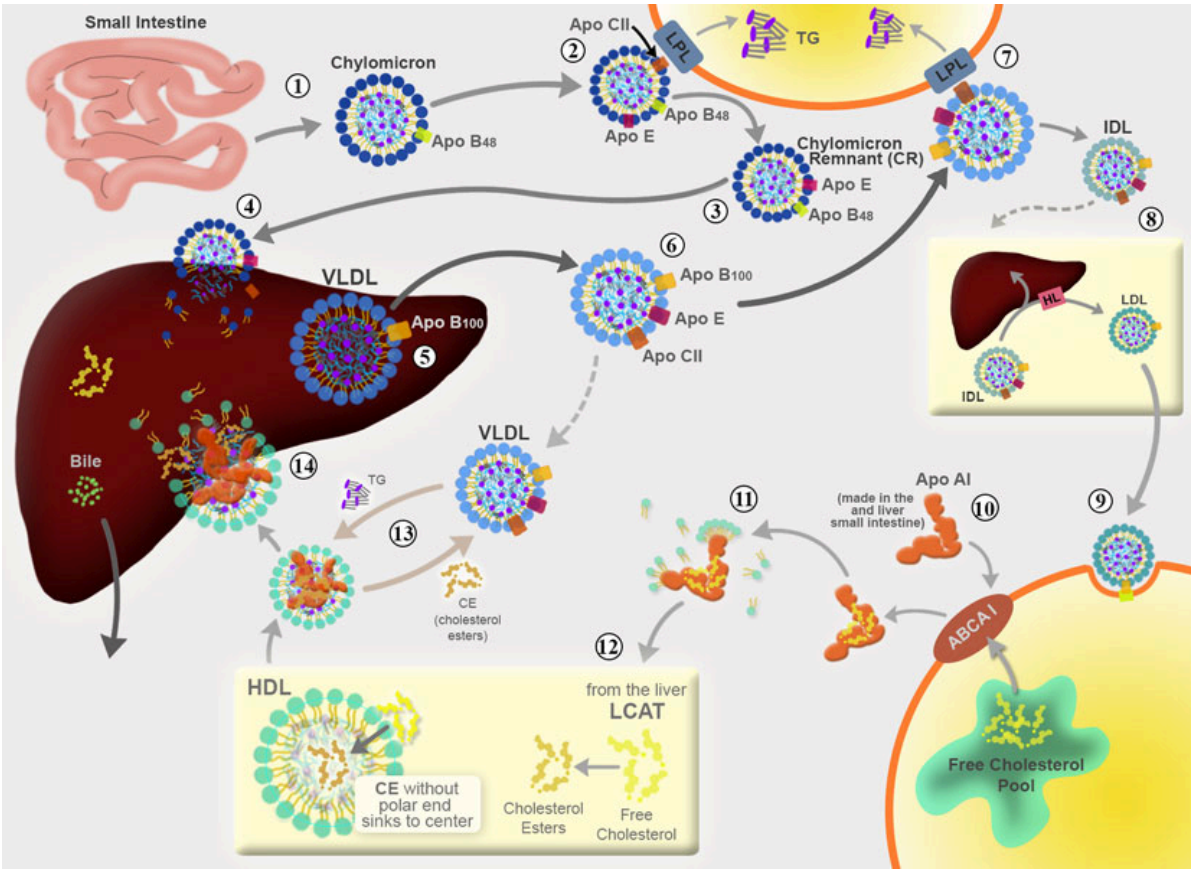

Image by BYUI student Tabitha D. 2015

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5.2.4 - Lipoproteins

To interpret the image above, match the numbers below

① Lipoproteins known as chylomicrons are made by enterocytes in the small intestine. They are made up of primarily triglycerides (80%) from dietary consumption. Contain Apo B48.

② Apo E and Apo CII are attached to the chylomicron in circulation from HDLs. Apo CII activates lipoprotein lipase receptors and the chylomicron is able to release a portion of its triglycerides into the body cell.

③ After the chylomicron releases a certain percentage of triglycerides (about 20%), Apo CII dissociates and the chylomicron has only Apo B48 and Apo E. This is called a chylomicron remnant.

④ Apo E recognizes the LDL-R on the hepatocytes and is then taken up where the rest of the lipids are used by the cell.

⑤ VLDLs are made in the liver and secreted with Apo B100.

⑥ VLDLs interact with HDLs and get Apo E and Apo CII.

⑦ Apo CII on VLDLs activate LPL-R on body cells and the VLDL releases triglycerides.

⑧ After dumping triglycerides into cells, VLDLs get smaller and are called IDLs. About 50% of the IDLs will loose even more triglyceride by interacting with another type of lipoprotein lipase called hepatic lipase (HL) on the liver. The other 50% of the IDLs will not interact with HL but will interact with receptors for APO E and will get absorbed by the liver cells. The 50% of the IDLs that interact with HL will get smaller and will lose their Apo CII and their Apo E and will have only their Apo B 100 left. These will now be called LDLs. LDLs interact with LDL receptors on body cells that need cholesterol. This interaction triggers endocytosis which pulls the LDL into the cell where it is dismantled to release cholesterol to the cell interior.

⑨ Lipoprotein Apo AI is made by enterocytes in the digestive tract and the liver. Apo AI attaches to membrane receptor ABCAI and gather free cholesterol from the cell's cholesterol pool.

⑩ Phospholipids begin to form around the Apo AI as it circulates.

⑪ Apo AI activates LCAT from the liver. The LCAT enzyme converts free cholesterol to cholesterol esters. This makes the cholesterol much more hydrophobic and it falls to the center of the growing HDL and is carried as a lipid core and the HDL becomes spherical.

⑫ The circulating HDLs meet up with VLDLs and chylomicrons and exchange cholesterol for triglycerides. The VLDLs receiving cholesterol esters grow in size and the HDLs that receive triglycerides shrink.

⑬ The HDL is then absorbed into the liver.

The two major types of lipoproteins listed above are low-density lipoproteins (LDL, IDL, vLDL) and high-density lipoproteins (HDL). In common literature these proteins are referred to as "good" (HDL) cholesterol and "bad" (LDL) cholesterol. Although not exactly accurate, the names have stuck and seem to be an effective way of transmitting information to the general public. The good and bad refer to the effects of the lipoproteins on cardiovascular health. At the most basic level, HDLs take lipids (i.e. cholesterol) from the tissues to the liver so that the liver can modify the cholesterol for excretion (a good thing). The LDLs take lipids from the liver for delivery to the tissue, also a good thing, because cells need lipids to repair membranes etc.

However, the stigma "bad" comes when there is an overabundance of the LDLs in the blood. If the blood concentration of LDLs is too high, then when cells signal for lipid delivery they get overwhelmed with LDLs. The excess LDLs accumulate in the walls of the blood vessel and become oxidized. To help clear out the excess LDLs white blood cells are recruited and engulf the LDL's. Once these cells phagocytose the LDL they have a foamy appearance and are thus called foam cells. These foam cells release cytokines which triggers an inflammatory response, attracting other macrophages and eventually resulting in the formation of a plaque in the wall of the blood vessel. These plaques bulge into the lumen of the blood vessel and restrict blood flow. If they become too extensive they can rupture initiating the coagulation cascade and completely stop blood flow through the vessel. This is the most common cause of a heart attack. What is the take home message? While both HDLs and LDLs are required for normal cardiovascular health, excess LDLs can be very detrimental.

Still, not everyone agrees with the high LDL to high cardiovascular risk disease hypothesis. Scientists arguing against the hypothesis cite data suggesting that high LDL or low LDL are not always correlated with cardiovascular disease. Consider these examples:

- Some patients that have heart attacks have low LDLs
- Elderly people with high LDLs live the longest
- Statin (cholesterol lowering drugs) are highly variable on their effectiveness against cardiovascular disease, but all of them lower LDLs

Recently a stronger correlation with a modified type of LDL called lipoprotein a (Lpa) has been strongly implicated in cardiovascular risk. Lpa is an LDL variant the consists of an LDL particle covalently attached to a glycoprotein called apolipoprotein B. This modification causes Lpa to last longer in the blood and gives the molecule the ability to interfere with blood clotting cascades. The enzymes responsible for this modification are determined genetically and don't appear to be correlated with other risk factors (ie obesity, smoking). Simply put, the amount of Lpa particles floating around in your blood is determined by genetics, but one thing appears to be sure, if you have lots of them, your chances of developing early cardiovascular diseases is greatly increased, independent of your good or bad cholesterol levels! As you can imagine, therapeutic drug treatment to target the production of Lpa molecules is a hot ticket item!

Back to traditional LDLs, there seems to be a trend in the literature connecting increased LDL's to trans fat consumption. This is most likely due to the effects of trans-fats on the liver. The liver produces lipoproteins and it does so in response to dietary triacylglycerol.

Thus, consuming trans-fats decreases the amount of "good" HDLs and increases the amount of "bad" LDLs, a lethal combination. But wait, aren't manufactures required to label the amount of trans-fat in their products? Yes, but this labeling can be misleading because the government regulations require that if a serving size as less than 0.5grams of trans fat it can be labeled as 0 grams trans-fat. Here is a general rule, if the ingredient list shows partially hydrogenated or fully hydrogenated in it, then the product has some amount of trans-fat.

The next item you should check is the serving size. If the serving size says 1 then the product should contain less than 0.5g. If the serving size is 35 and you eat 25 servings…. well…you may have other issues. At any rate, the table below shows some common foods and their estimated trans-fat amounts. Why use trans-fat in your product? Well try having a competition at home making a pie crust or baked homemade cookies with Butter vs Crisco. There is really no competition, Crisco laden cookies and pie crust simply taste better, their texture is better and they never go bad. This is why we use trans-fats, they make food taste better and last longer.

Here are some videos made in our department that walk through the stories of lipoproteins. Spending some time with these videos can really help:

https://youtu.be/NoupEo5eB5U

https://youtu.be/B2rOqe8e75E

https://youtu.be/PQcJRvbBI8M

**FYI - Here is an excellent article on the subject of Lipoproteins if you would like to read more

https://www.ncbi.nlm.nih.gov/books/NBK305896/