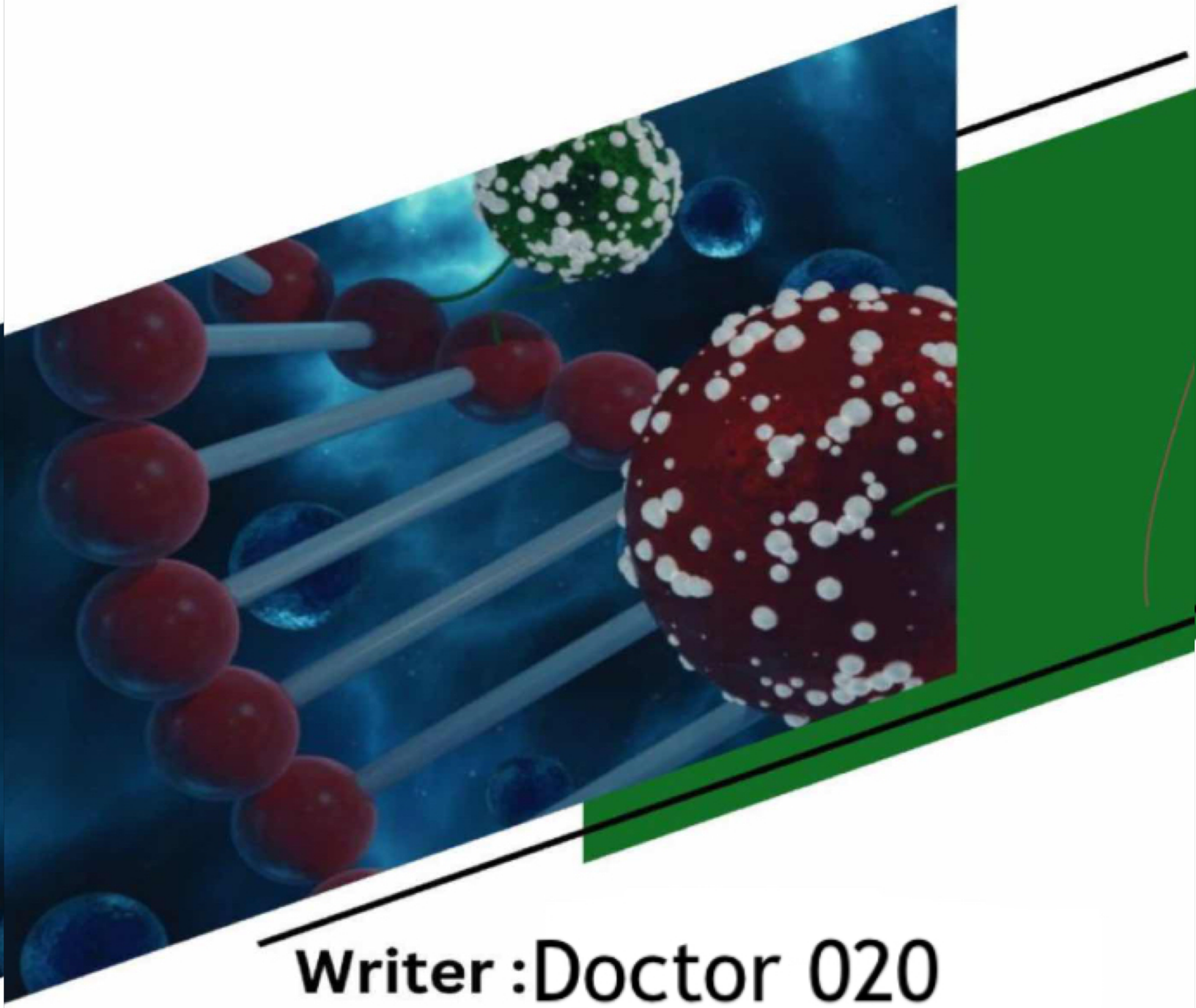
Doctor 021

METABOLISM

Sheet no. 26



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CHARACTERISTICS OF LIPOPROTEINS:

So, Lipoproteins we have talked about them in the last lecture and their main functions are to:

1. Solubilize and carry plasma lipids: as we all know that lipids are hydrophobic, so they tend to cluster in the blood unless they have a carrier protein, for ex: albumin, so the lipoproteins they solubilize the lipids in the hydrophilic blood

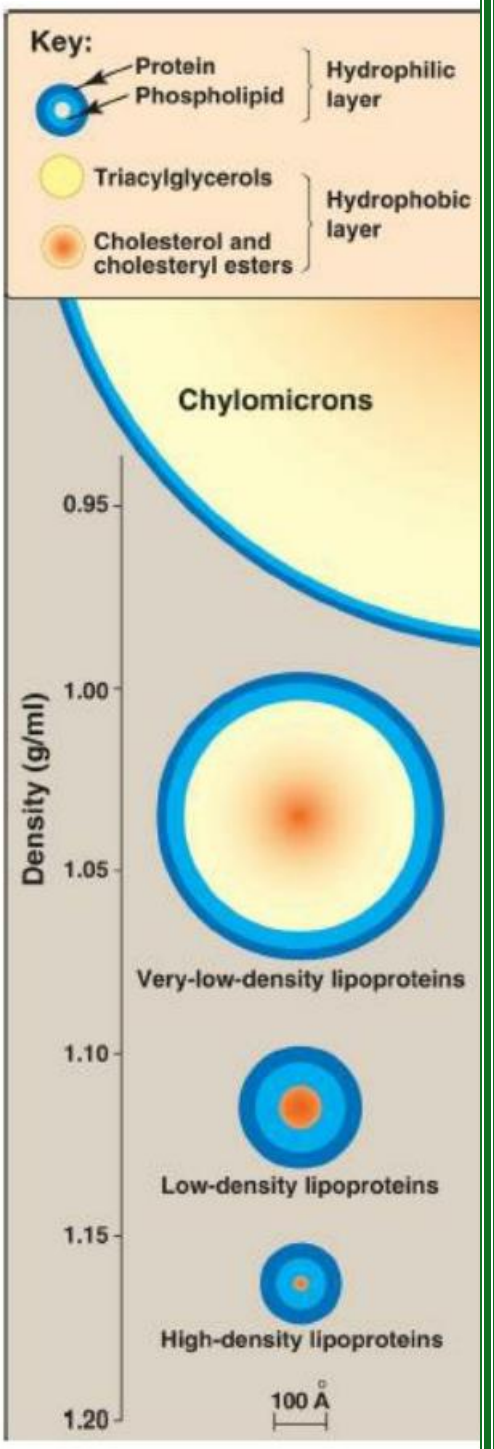
2. Transport lipids from one tissue to another

These lipoproteins vary in size, so you have chylomicrons being the largest and HDL being the smallest

Also they differ in density (which is the ratio of proteins to lipids), so chylomicrons have the lightest density cuz they have a lot of lipids compare to proteins, HDLs on the other hand have the highest density cuz they have higher amount of proteins comparing with lipids

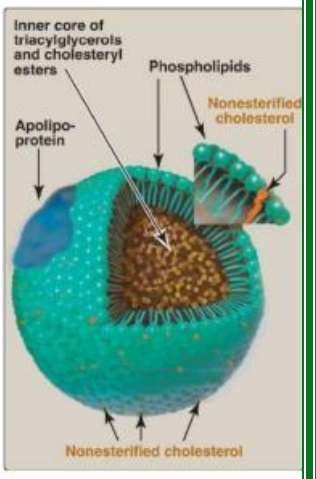
They differ in lipid content, so chylomicron have a lot of TAGs relative to cholesterol, same thing with VLDL. HDLs and LDLs on the other hand carry a lot of cholesterol esters

They differ in function as well, Chylomicrons carry dietary lipids from intestinal cells to the liver, while HDLs carry esters from peripheral tissues back to liver. PAY ATTENTION TO THESE DIFFRENCES PLEAS!!



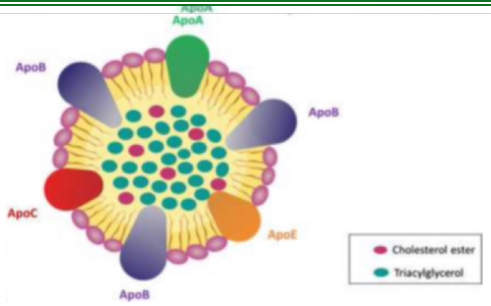
☙COMPOSITION OF LIPOPROTEINS:

- Now, these lipoproteins also differ in the type of proteins they carry these proteins are known as **APOLIPOPROTEINS** and they are **AMPHIPATHIC**. They exist on the surface of these lipoproteins, the hydrophilic part is on the outer surface, while the hydrophobic is on the core
- Some lipids are amphipathic such as cholesterol which contains hydroxyl group (these amphipathic lipids will have their hydrophilic regions on the surface while other hydrophobic regions will be hidden inside) and there are other lipids that are completely hydrophobic such as cholesterol esters & TAG



- A neutral lipid core (containing TAG and CHOLESTEROL ESTERS) surrounded by a shell of amphipathic apolipoproteins, phospholipids, and non-esterified (free) cholesterol. Cholesterol If it is not esterified the (OH) group which is the hydrophilic part is exposed to the outside.
- They also differ in the sources of lipids, either they have a dietary lipids which are known as EXOGENOUS SOURCE in which the lipids are taken from intestinal cells to liver, and we have ENDOGENOUS lipids which are synthesized de novo (by itself) from liver to peripheral tissues or back from tissues like adipose tissues to liver
- Well, the three major cholesterol carriers are HDL, LDL and VLDL to some extent, except that the VLDL carries five times more TAGs verses CHOLESTEROL
- So, in order to calculate how much CHOLESTEROL is there in the blood, we find the summation of the amount of cholesterol that is present in LDL, HDL and VLDL. *
  - NOTE: VLDL -C is calculated by dividing VLDL- TAG by 5 because the TAG/cholesterol ration is 5/1 in VLDL.

The goal value for total cholesterol is <200 mg/dl.



APOLIPOPROTEINS:

functions :-

1- Recognition sites for cell-surface receptors

2- They also act as activators or coenzymes for enzymes involved in lipoprotein metabolism, so they interact with enzymes for ex: lipases on the surface of endothelial cells and these enzymes get activated.

- Now, some of them are essential, so without them there would be no lipoprotein like; Apo- B 48, Apo -B 100 and Apo A 1 , they are structural molecules that are necessary for the formation of lipoproteins.(Can't be removed) (structural components)
- Some of the can be transferred freely from one lipoprotein to the another one
- Classes of lipoproteins are denoted by letters, and subclasses are designated by ROMAN numbers.

Ex: Apolipoprotein [apo] C-I, apo C-II and apo C-III, so there us a variance even with the same lipoprotein.

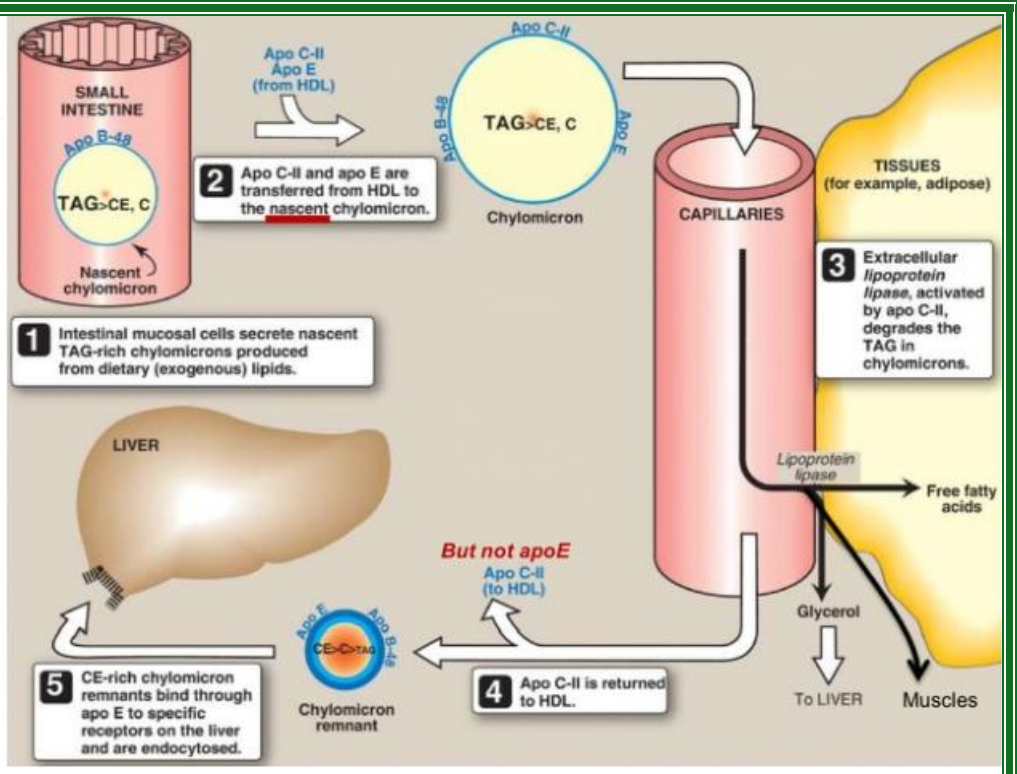
Don't memorize this table, just focus on the mentioned in this sheet

Apolipo-protein	Molecular Weight	Chylomicron (CM)	VLDL	IDL/CM remnants	LDL	HDL
AI	28,016	Ex	Ex			St
AII	17,414	Ex	Ex			Ex
B100	515,000		St	St	St	
B48	241,000	St*		St*		
CI	6600	Ex	Ex			Ex
CII	8800	Ex	Ex			
CIII	8750	Ex	Ex	Ex		Ex
E	34,100	Ex	Ex	Ex		Ex

*B48 is exclusive to chylomicrons and chylomicrons remnants. St, structural apolipoprotein; Ex, exchangeable apolipoprotein. Other apolipoproteins (AIV, AV, D, F, G, H, J, (a)) are beyond the scope of this review.

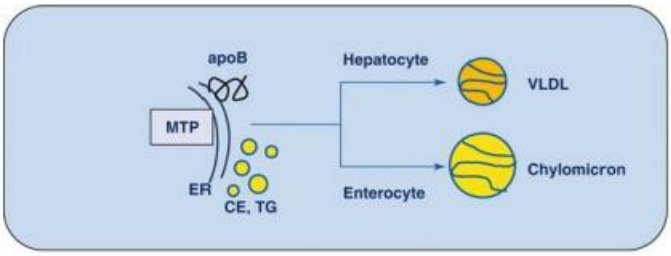
- لازم تعرف الـ proteins موجودين بأي Lipoprotein وايش الـ Function تبعهم
- من غير أرقام

Microsomal triglyceride transfer protein (MTP) assembles the apoB protein with the lipids in the ER before transition to the Golgi, where the particles are packaged in secretory vesicles



CHYLOMICRONS : (explanation of the figure below)

They are synthesized in the intestinal cells, so it starts with complexing apo-b 48 with the lipids: TAG, CE and phospholipids (that are absorbed by intestinal cells). And in order to accumulate to complex these different components, you need a protein known as MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN (MTP), which exist not only in the intestinal cells but exist in the hepatocyte as well and in both places, it does the same function of formation of the lipoprotein chylomicron in the intestinal cells, VLDL in the hepatocyte



What thus protein does (MTP) it assembles the apoprotein (like apo- b 48) with the lipids in ER where it has been formed and then it transits to the Golgi (apolipoproteins gets glycosylated there) the particles are packed in secretory vesicles and go from golgi to the outside, into the lymphatics then it dompts in the blood and so on

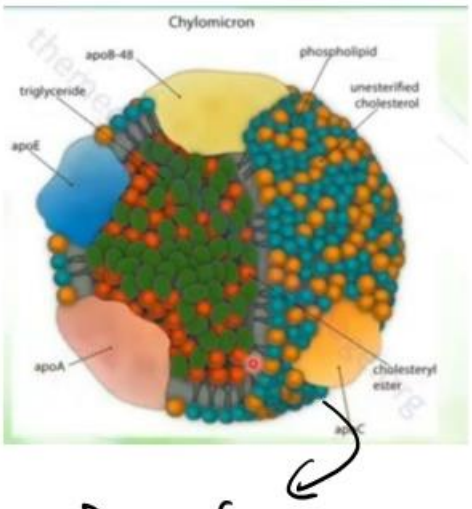
- Once you have the release of chylomicrons from intestinal cells, now we have chylomicrons that has Apo-b 48 (48 refers to the relative size of the protein because it is formed in the same gene that forms Apo -b 100 in VLDL in hepatocyte, and what happened is a gene editing)
- We have this chylomicron, which Known as nascent (premature) which means that it is not functional yet, and in order to get a function chylomicron you need additional apolipoproteins which are Apo-C ll and Apo-E and these proteins are transferred from HDL to the chylomicrons.
- Now, we have this chylomicron containing three Apolipoproteins (Apo-b48, Apo- C ll and Apo -E), and they move in the capillaries and blood vessels, in which there are lipoprotein lipases on the surface of its endothelial cells which are synthesized by adiposities and muscle cells. Now this lipase needs Apo C ll to be active, so it interacts with the ApoC2 on the surface of chylomicrons, and if it becomes active it starts releasing fatty acids that exist on the TAGs primarily, as well as phospholipids and enter the tissues. NOTE: for MUSCLE CELLS they use these fatty acids for energy purposes while ADIBOCYTE use them for storage in the form of TAGs.
- So, as these fatty acids are released, the chylomicrons get smaller and smaller and they are converted into chylomicron remnants
- Now, right before the formation of chylomicron remnants, you have the release of Apo c ll which will go back into HDL, and by that we end by chylomicron remnant containing only two Apolipoproteins which are Apo b 48 and Apo E. Apo E is important to chylomicrons to reach liver cells which have a Apo E receptor on their surfaces , so after binding these chylomicron remnants will get into the liver tissue .

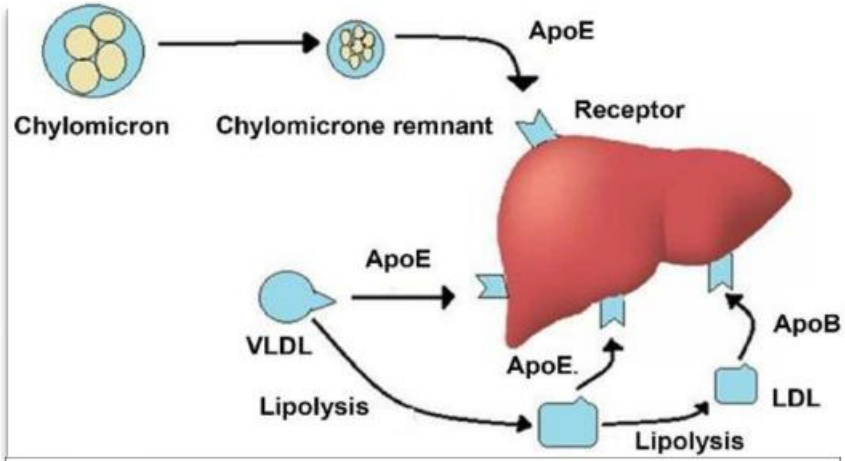
FATES OF CHYLOMICRONS:

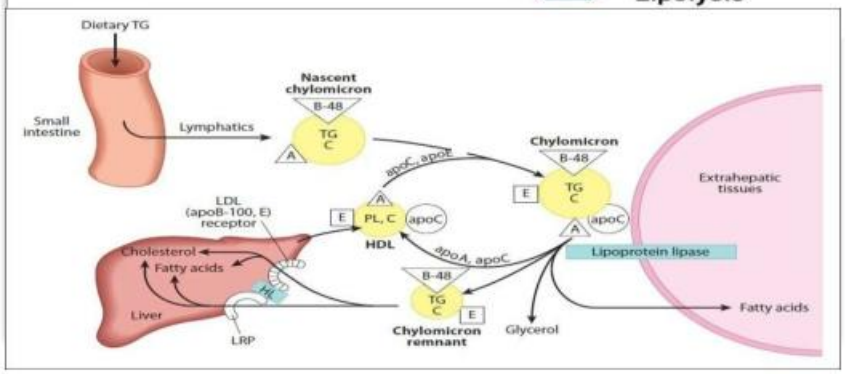
When TAGs are removed, chylomicron remnants would contain cholesterol esters, phospholipids, apolipoproteins, fat- soluble vitamins, and a small amount of TAGs.

Chylomicron remnants bind to ApoE receptors on the liver cell and get endocytosed (receptor mediated endocytosis)

The intracellular remnants are hydrolyzed to their component parts.







Just For showing

Type I hyperlipoproteinaemia which is deficiency in the LPL and apo c-II ,so lipases are defective and chylomicrons will not shrink (no chylomicron remnants) ,familial chylomicronemia, hypertriglyceridemia; Deficiency of LPL or apo C -II leading to the accumulation of chylomicron -TAG in the plasma.

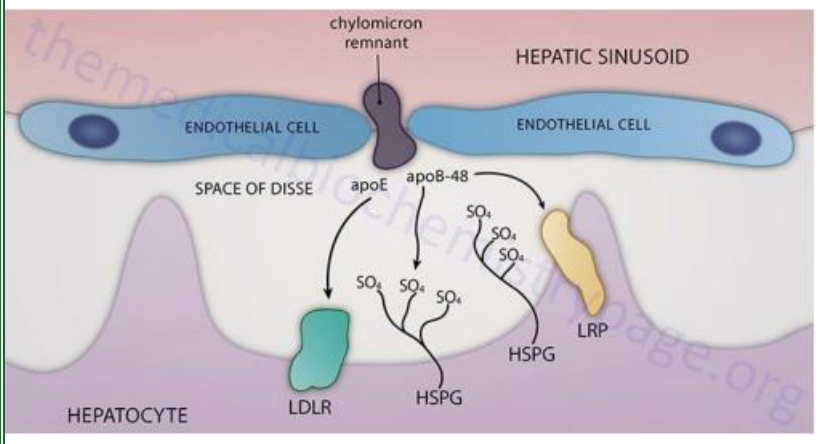
♡ صلى الله على سيدنا محمد ♡

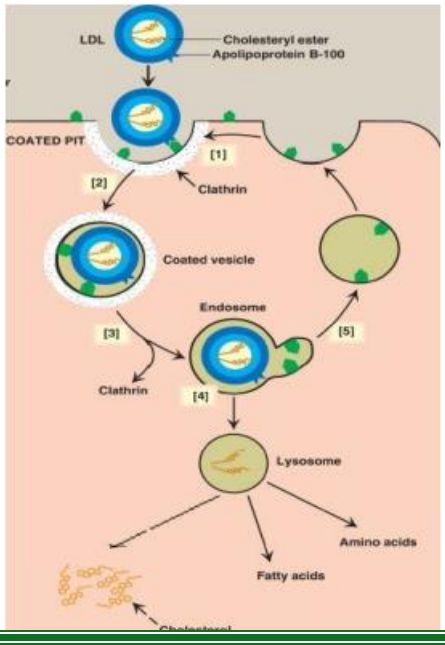
THE UPTAKE OF CHYLOMICRON REMNANTS:

- So, again the chylomicron remnants bind to ApoE receptors that are present on certain regions on the plasma membrane of the hepatocytes called **lipid drafts** which are rich in signaling receptors cluster on one area on the plasma membrane and inside the cytosol like **RAS** for ex, exist on lipid drafts.
- So, after binding there would be internalization of the chylomicron remnants and formation of vesicles which will be converted into endosomes by binding of certain protein. Now, these endosomes have a low pH (6.5) and that allows the dissociation of the chylomicron remnants from the ApoE receptor, which will be recycled back to the plasma membrane and the endosome will be transformed into lysosome which have an even lower PH (5 -5.5) and this allows for the denaturation of proteins , as well as lipids and an activation of hydrolytic enzymes (proteases, glycosidases, lipases and ,so on) which degrade these macromolecules ,so proteins will release amino acids into the cytosol , same thing with cholesterol ,same thing with fatty acids which will be used as nutrients for the use of the cells .

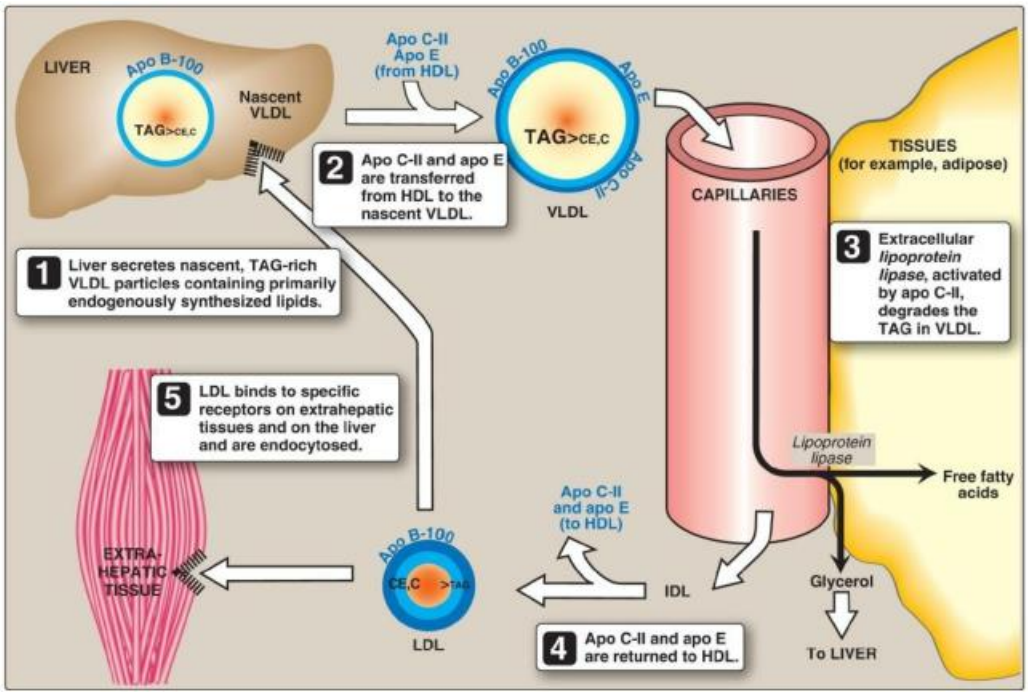
Note: these vesicles are also known as phagosomes and the lysosomes would be phagolysomsomes

- Type lll hyperlipoprotenemia: mutation in ApoE gene, so it is defective and will not bind to its receptor, so there would be accumulation of **chylomicron remnants** .





VERY LOW DENSITY LIPOPROTEIN:



- **These VLDL are synthesized in the liver as nascent VLDL (premature, non-functional yet) and are formed by Apo b 100 (it is produced from the same gene as Apo b 48 except that now we have a larger protein)**
- **VLDLs actually carry Endogenous lipids, which are lipids that are synthesized in the liver or transported from adipocyte, so now you have the release of VLDL from the hepatocyte, and they gain apo c ll and apoE from HDL just like chylomicrons, the only difference here is that VLDL carry endogenous lipids and have apo b 100 while chylomicrons carry dietary lipids and apo b 48, as well as the route of the transport**
- **VLDL contain Apo b100, apo c -ll and ApoE, so it goes into the capillaries, same thing you have apo c ll, it activates the lipoprotein lipase on the surface of endothelial cells, then fatty acids would be released same as before**
- **Then VLDL will become sort of free from TAG (glycerol (hydrophilic) would be released from VLDL to the blood), and it would be transformed into IDL (intermediate between VLDL and LDL) then IDLs might release apo c-ll and apoE forming LDL while in the case of chylomicron only apo c-ll**

LDL are IDL without apoC2 and apoE

So, now we have LDL that has apo b100 and it is rich with cholesterol esters but it doesn't have TAGs, they travel to peripheral tissues and release cholesterol esters into peripheral tissues like muscle

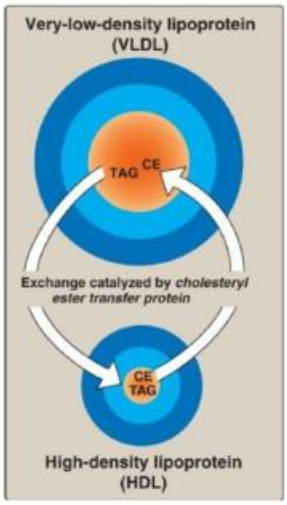
Two conditions are related with the deficiency if functional VLDL:

1. **one is known as non-alcoholic fatty liver (hepatic steatosis) in which the hepatic synthesis of TAGs is >> VLDL release, so you have the liver that is rich with TAGs that are not carried by VLDL because there are not enough VLDL particles**
2. **the other condition is Abetalipoproteinemia: which is a rare hypolipoprotenemia caused by defective MTP, leading to deficiency in the formation of VLDL or chylomicrons and TAGs accumulate in the liver and the intestine.**

   Also the person with this condition will have a deficiency fat-soluble vitamins because there are no chylomicrons and VLDL to carry them.

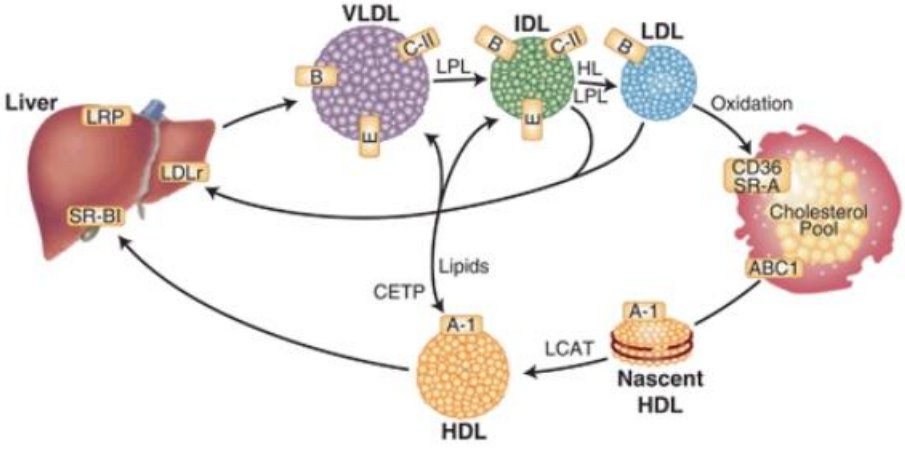
③

HDL



IDL and LDL

Roles of lipoproteins



This figure is explained in the next page

Relation of VLDL to HDL, IDL, and LDL:

- There is something interesting that takes place in the blood, sort of like commercial exchange between VLDL and HDL and that is both of the travel in the blood, they meet halfway and they exchange lipid content, so HDL releases cholesterol esters to VLDL, and VLDLs gives TAGs to HDL, this process is catalyzed by a protein kwon as cholesterol ester transfer protein (CETP). There is also a relationship between IDL and LDL, as we have said before, we have the release of VLDL from the hepatocyte these have the three types of apolipoptroteins apo c-ll, b 100 and E and you have the release of fatty acids from the TAGs
- you have the conversion of VLDL into IDL (VLDL after releasing fatty acids), now IDL has apo c-ll and apo b 100 and apo E as well , and this IDL can also carried back to the liver and binds to apo E receptor just like chylomicron.
- Now, If you have the release of apo c -ll and E from IDL it becomes LDL having b 100 only and it carries alot of cholesterol esters into the peripheral tissues .

REGULATION OF LIPOPROTEIN LIPASE (LPL):

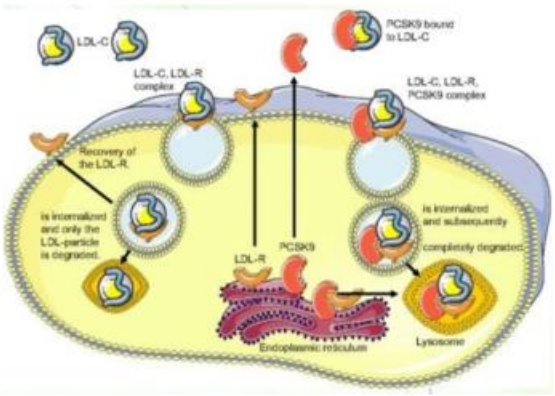
- LPL is synthesised in the peripheral tissues by adipose tissue and by cardiac (have a lot of lipases comparing with other tissues because cardiac muscle relies a lot on aerobic metabolism and fatty acid metabolism specifically) and skeletal muscle. (the highest concentration of LPL is in cardiac muscle).
- Expression of the tissue-specific isozyme is regulated by nutritional state and hormonal level.
- tissue -specific lipoprotein lipase is regulated hormonally.
- In the fed state (elevated insulin levels),LPL synthesise is increased in adipose (producing a lot of lipases which will lead to releasing of a lots of fatty acids and store them as TAGs) but decreased in muscle tissue.

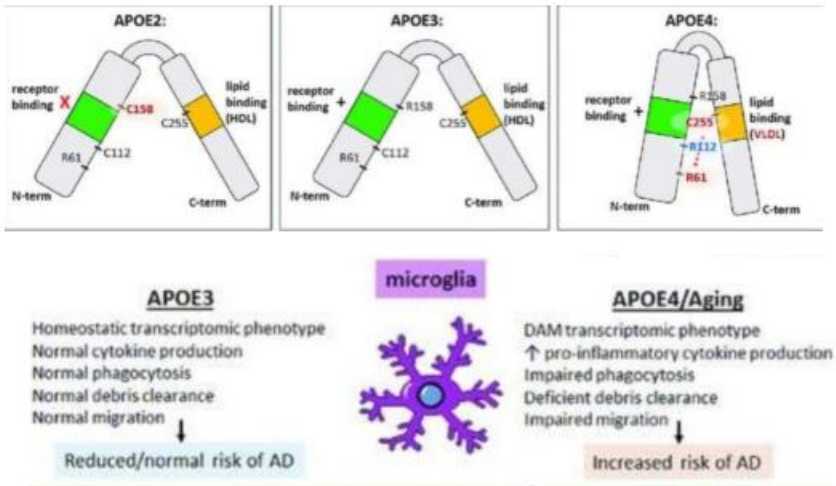
- Fasting (decreased insulin) favors LPL synthesis in muscle.(in this case skeletal muscle overexpresses lipoprotein lipases in order to produce energy).

A note about apoE:

- ApoE is present in three isoforms, E-2 (the least common but if you an individual who is homozygous to this isoform, they are at risk of having atherosclerosis and heart attacks because apoE-2 binds poorly to receptors ,so there is an amino acid varient or gene varient that produces this apoE-that doesn't bind strongly, so you will have a lot if chylomicrons and VLDLs which transformsing LDL in blood which increases the risk of atherosclerosis), E-3 (the most common) ,and E-4.
- ApoE-2 binds poorly to receptors.
  - Patients who are homozygotes for apoE-2 are deficient in the clearance of IDL and chylomicron remnants.
  - These individuals have familial type lll hyperlipoproteinemia (familial dysbetalipoproteinemia or broad beta disease) , with hypercholesterolemia and premature atherosclerosis
- The apoE-4 isoform confers increased susceptibility to an ealier age of onset o the late onset firm of Alzuhimer disease .
- Homozygotes being at greatest risk .

LOW DENSITY LIPOPROTEIN :



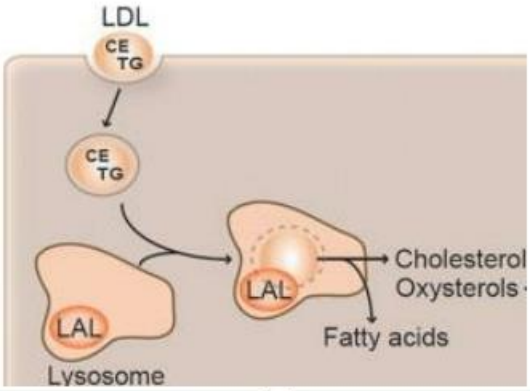


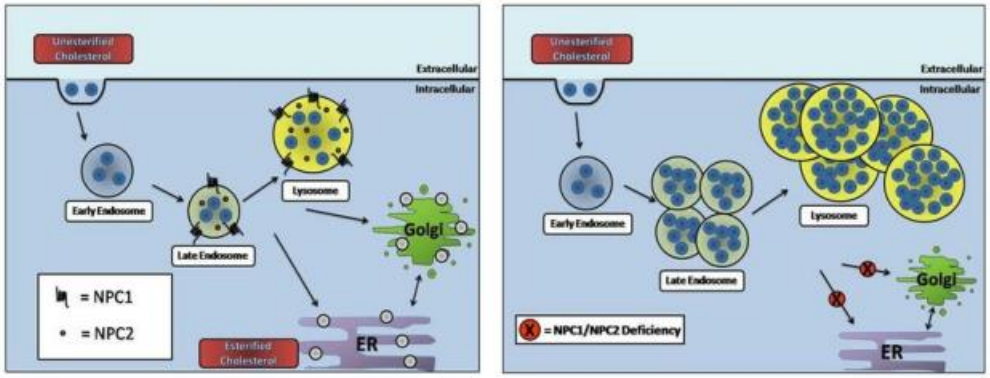
- LDL they are formed from VLDL after losing the apo c-ll and apoE
- Primary lipoprotein is B-100
- Plasma cholesterol ~70% of LDL content, is taken to peripheral tissues.
- It has its own LDL receptor on the surface of peripheral tissues and liver as well and get internalized by Receptor-mediated endocytosis
- Type lla hyperlipidaemia (familial hypercholesterolemia [FH]): reduced synthesis of functional LDL receptor leading to premature atherosclerosis. (these individuals die at late teens) (autosomal recessive)
- Defective apo B-100: autosomal dominant hypercholesterolemia with reduced binding to LDL receptor.
- proprotein convertase subtilisin /kexin type 9 (PCSK9) promotes internalization and lysosomal degradation of the receptor(it is an interesting protein (protease), so what it does is the following , it is released from cells and binds to LDL and when LDL binds to its receptor they are both internalized; LDL ,PCSK9 and of course the LDL receptor ,so they are internalized except that the receptor is not recycled back to the plasma membrane ,it goes with LDL to the lysosomes , so this receptor will be degraded ,so you don't much receptor on the cell surface ,so pcsk9 is a bit dangerous ,that high levels of it can result in atherosclerosis .
- PCSK9 inhibitors are now available for the treatment of hypercholesterolemia

LYSOZOMAL STORAGE DISEASE:

- Wolman disease: a severe autosomal -recessive deficiency of lysosomal acid lipase deficiency leading to massive intracellular accumulation of cholesterol esters and TAGs.
- Niemann-pick disease ,type C :autosomal -recessive deficiency in the transport of free cholesterol out of the lysozome inti ER.
- Both are related to the metabolism of cholesterol

Figures on lysosomal storage Diseases



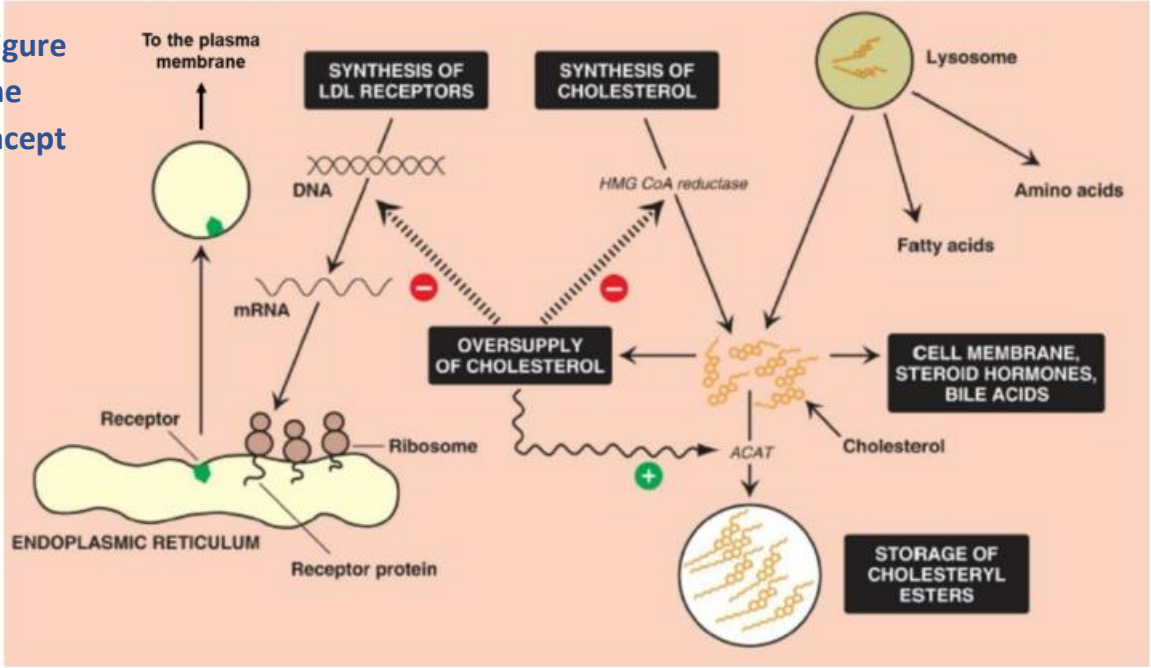


FATE AND EFFECTS OF CHOLESTEROL:

- **High intracellular cholesterol levels:**
  - **Inhibit de novo cholesterol synthesis**
  - **Inhibition if gene expression, high cholesterol thus SREBP-Will not go out ER.**
  - **Induce the degradation of HMG Co-A reductase**
  - **Decrease the synthesis of LDL receptor is reduced through the negative regulation of SREBP-2 (because there is a harmony so It is the same transcription factor regulating the expression of reductase which responsible of cholesterol synthesis and LDL receptor which is responsible for taking LDL into cell)**
  - **Enhance the activity of acyl CoA cholesterol acyltransferase (ACAT) which is responsible for esterifying excess cholesterol**

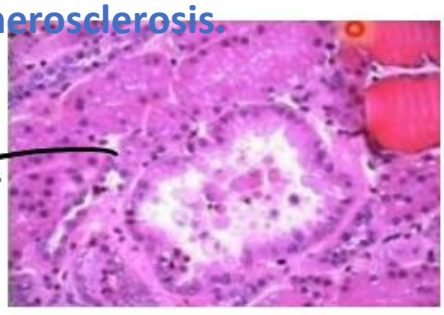
So, that makes sense, If we have a high amount of cholesterol, so let's make more cholesterol esters which can be stored in the cells

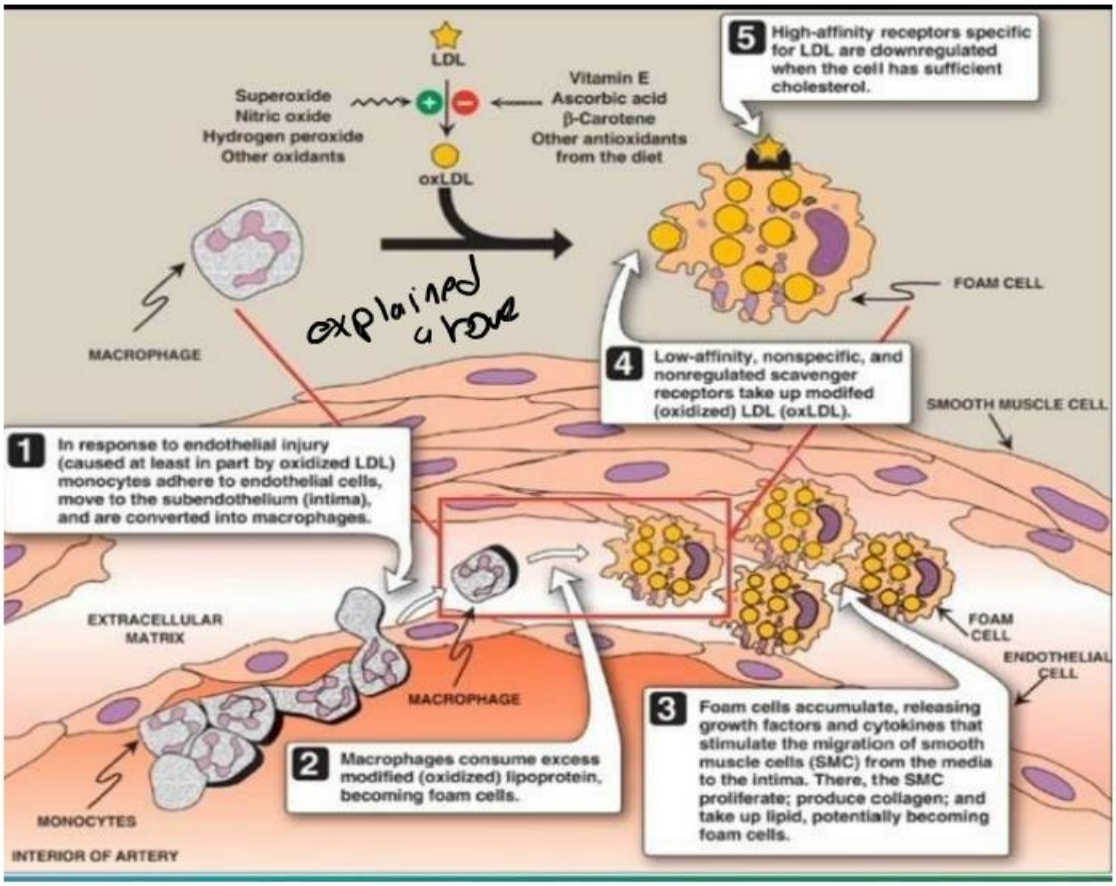
Link this figure with the above concept



FOAM CELLS:

- Macrophages possess high levels of unregulated of scavenger receptor class A (SR-A) that can bind, induce endocytosis of LDL particles (without getting enough because they are not regulated) carrying oxidized lipids or apo B proteins
- Cholesteryl esters accumulate in macrophages, which transform into foam cells (the problem with these foam cells is that they cluster in the blood forming clots, which increases the risk of) atherosclerosis.
- Macrophages have their own LDL receptor but they also have a scavenger receptor these can take everything that are in surrounding environment, such as LDL from the blood.
- LDL is called bad cholesterol, because it transfers Cholesterol from the liver to the peripheral tissues, and because they aggregate (cluster) in the blood, so it contributes to increasing the risk of atherosclerosis.





HIGH DENSITY LIPOOROTEIN:

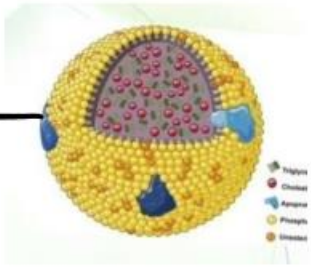
- **HDL particles are formed by the addition of lipids to apo A-1 (~70% of lipoproteins in HDL), which is synthesized by the liver and intestine.**

FUNCTIONS:

- **HDL provides apo C ll and E to VLDL and chylomicron remnants**
- **They take up cholesterol from peripheral tissue and return it to the liver as cholesteryl esters. (good cholesterol).**
- **Their higher content of PC (phosphatidylcholine) enables them to carry non- esterified cholesterol.**

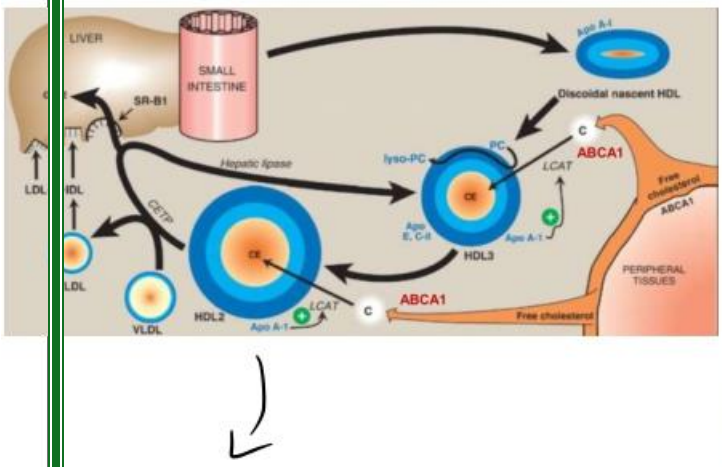
Note: PC is responsible of transferring fatty acids from phospholipid to cholesterol.

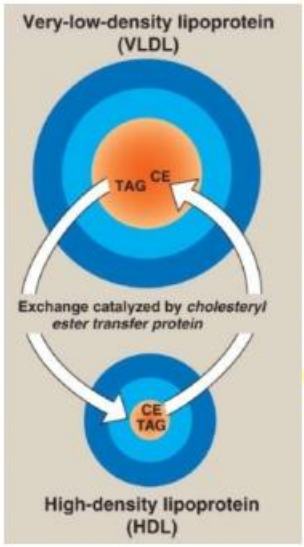
HDL



TRANSPORT OF CHOLESTEROL BY HDL

VLDL ⇌ HDL Throug CETP

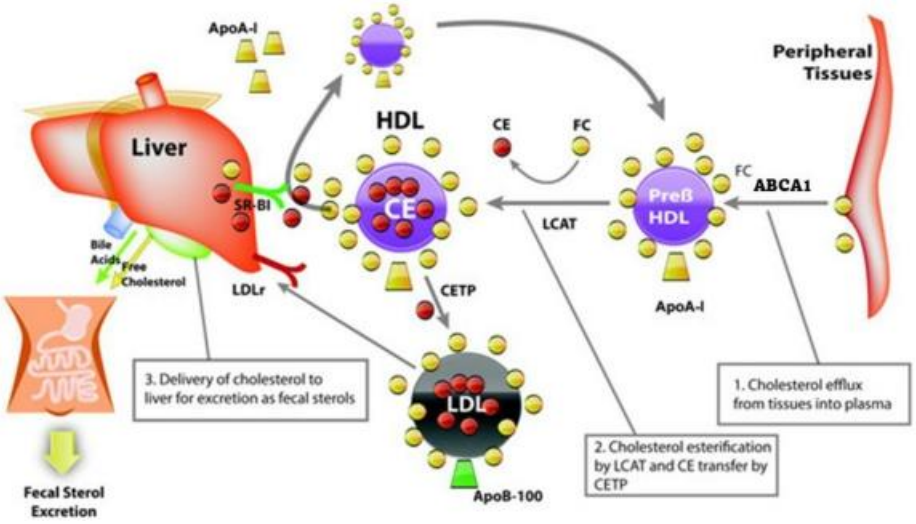




Some TAGs are transferred from VLDL to HDL in an exchange reaction that concomitantly transfers cholesteryl esters from HDL to VLDL.
This exchange is accomplished by cholesteryl ester transfer protein (CETP).
End-result is relieving product inhibition of LCAT.
VLDL can then be converted to IDL and LDL.

- **The liver synthesized, nascent HDL bound plasma enzyme lecithin cholesterol acyltransferase (LCAT or PCAT), (lecithin is the other name of phosphatidyl choline) a liver enzyme , esterifies the HDL-carried cholesterol by transferring the FA of carbon 2 of PC and CE is sequestered in HDL in the HDL cire.**
  - **LCAT is activated by apo A-1**
  - **lysophophatidycholine is carried by by albumin. (formed after phosphatidyl choline loses a F.A on carbon n 2)**
- **Hepatic lipases, which degrades TAGs and phospholipids, participated in the conversion of HDL2 to HDL3**
- **CETP transfers some of the cholesteryl esters from HDL to VLDL in exchange for TAG, relieving product of LCAT**
- **HDL is discoidal and have Apo A1. It carries cholesterol that comes from peripheral tissues, the HDL become spherical in shape but still lipid poor and at this stage it is designated as HDL3, as HDL carry more cholesterol and as cholesterol are esterified, it becomes HDL2 (lipid rich) and when cholesterol is esterified, they get right in the middle of HDL because they are quite hydrophobic so it stays away from the surface.**

REVERSE CHOLESTEROL TRANSPORT:



- The efflux of cholesterol from peripheral cells is mediated primarily by the transport protein ABCA1 (the normal transfer is from the liver to the peripheral tissues but this transport is the reverse ,and HDL is responsible for this process by carrying cholesterol from peripheral tissues back to the liver)

  But how the cholesterol gets transferred from the peripheral tissues into HDL ? well ,actually there is a pump kwon as ABCA1 pump. Now you have this HDL that has a cholesterol and it gets esterified (P.C ->C.E),and we end with HDL2 which has a lot of CE (at this point we have exchange with VLDL which will be converted into LDL) and it will get into the hepatocyte by a receptor in a different mechanism that that of both chylomicrons and LDL (which was by binding to a receptor followed by induction of receptor mediated endocytosis ,but that for HDL is by binding to a scavenger receptor class B 1(SRB1) on the surface of hepatocyte and pumps cholesterol inside liver cells
- Tangier disease (قنجط(no ABCA1, no HDL particles, degradation of apo A-1
- Cholesteryl ester by the liver is mediated by scavenger receptor* class B type 1 (SR-B1)

NOTE: Defective ABCA1 causes sitosterolemia ,cystic fibrosis, X-linked adrenoleukodystrophy ,respiratory distress syndrome, and liver disease (RDSS is related to surfactants)

V2

Page 17 : VLDL to HDL through CETP

V3

Page 7:-instead of phospholipase it is LPL