Plasma lipoproteins

By

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Plasma lipids

- In the fasting state (usually measured after12 hours) :

- The plasma total lipids ranges between 400-700 mg/dl
- The plasma total cholesterol : 140-200 mg/dl
- The plasma total phospholipids : 150-200 mg/dl
- The plasma total triacylglycerols: 50-150 mg/dl
- The plasma total free fatty acids (FFA): 10-20 mg/dl
- Minute amounts of steroid hormones , fat-soluble vitamins, and carotenoids.

- These lipids are found in plasma in the form of lipoprotein complex=plasma lipoproteins.

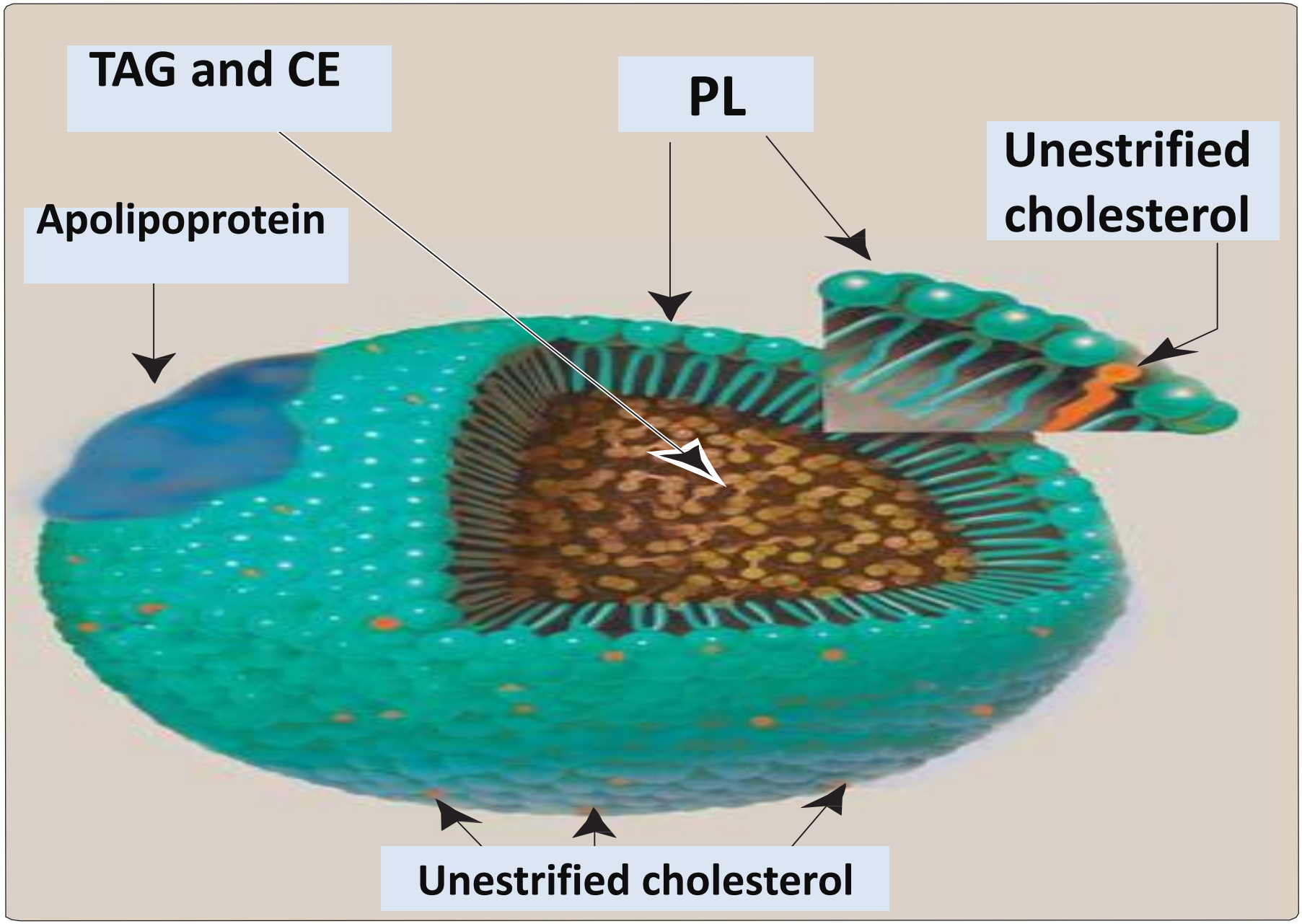
- The problem of transporting the hydrophobic lipids in an aqueous phase, the blood plasma, is solved by associating the insoluble (non polar) TAG and CE with the more soluble (amphipathic) PL,C, and proteins to form a **hydrophilic lipoprotein complex.**

- Each plasma lipoprotein particle contains:

1- A non polar core composed of TG and CE

2- A single layer of polar lipids (PL and C) together with proteins called **apolipoproteins**

❖ ***Amphipathic:*** *chemical compound possessing both hydrophilic (water-loving, polar) and lipophilic (fat-loving) properties*.


TAG and CE
PL
Unestrified cholesterol
Apolipoprotein
Unestrified cholesterol

- **Apolipoproteins** are either peripheral (can be transferred) or integral (can not be transferred).

- They act as **activator for enzymes** (e.g. **apo C II** activator for lipoprotein lipase) and are **important for receptor mediated uptake** of plasma lipoproteins by certain tissues (e.g. receptors for apo E in liver cells for uptake of chylomicrons).

Plasma lipoproteins:

Four major groups (fractions) of lipoproteins have been identified that are important physiologically and in clinical diagnosis. These are:

1- Chylomicrons (CM): They are derived from intestinal absorption of triacylglycerols and other lipids.

2- Very low density lipoproteins (VLDL, or pre-β-lipoproteins): They are derived from the liver for the export of triacylglycerols.

3- Low density lipoproteins (LDL or β-lipoprotein): They are representing a final stage for catabolism of VLDL.

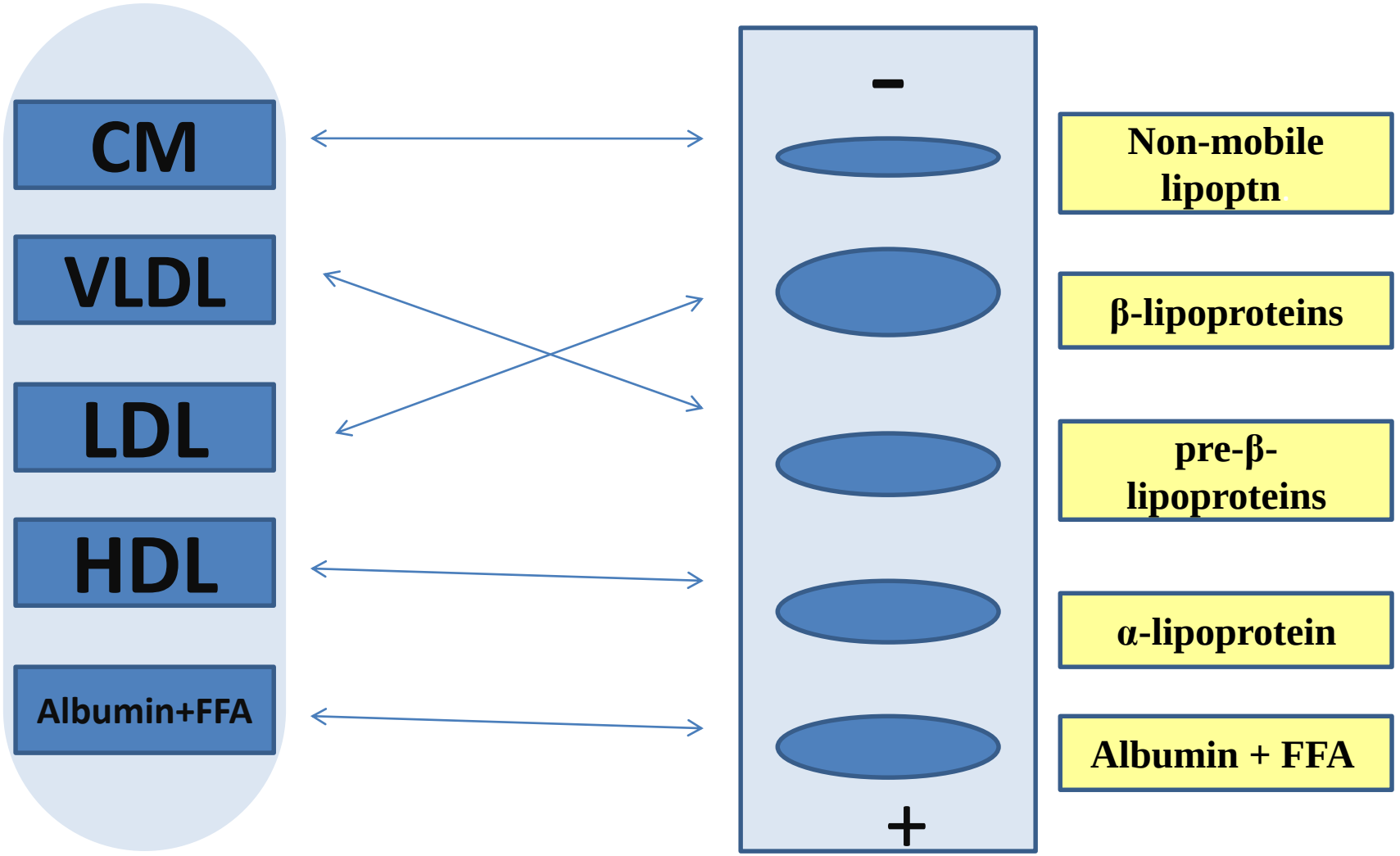
4- High-density lipoproteins (HDL or α-lipoprotein): They are involved in chylomicrons and VLDL metabolism as well as **cholesterol transport**.

5- Albumin + FFA (NEFA): FFA was carried by albumin.

- Plasma lipoproteins are separated into different fractions by two methods:

1- **Electrophoresis** (According to their mobility in electric field).

2- **Ultracentrifugation** : They are separated according to their **density**. The higher the protein content the higher the denisty of the particles.


CM
VLDL
LDL
HDL
Albumin+FFA
-
+
Non-mobile lipoptn
β-lipoproteins
pre-β-lipoproteins
α-lipoprotein
Albumin + FFA

Chylomicron metabolism

- **Origin:** Chylomicrons are assembled in intestinal mucosal cells.

- **Structure & Function:** They are chiefly composed of the absorbed TAG to which are added smaller amounts of CE, C, PL, and proteins. Their function is to transport TAGs to various tissues and cholesterol to the liver.

- **Nascent chylomicron** principally contain 2 types of proteins, **apo A** and **apo B-48**.

- The nascent chylomicron transported to the plasma via lymphatics where it is rapidly modified (converted to mature chylomicron) by receiving **apo E** and **apo C** from **HDL**.

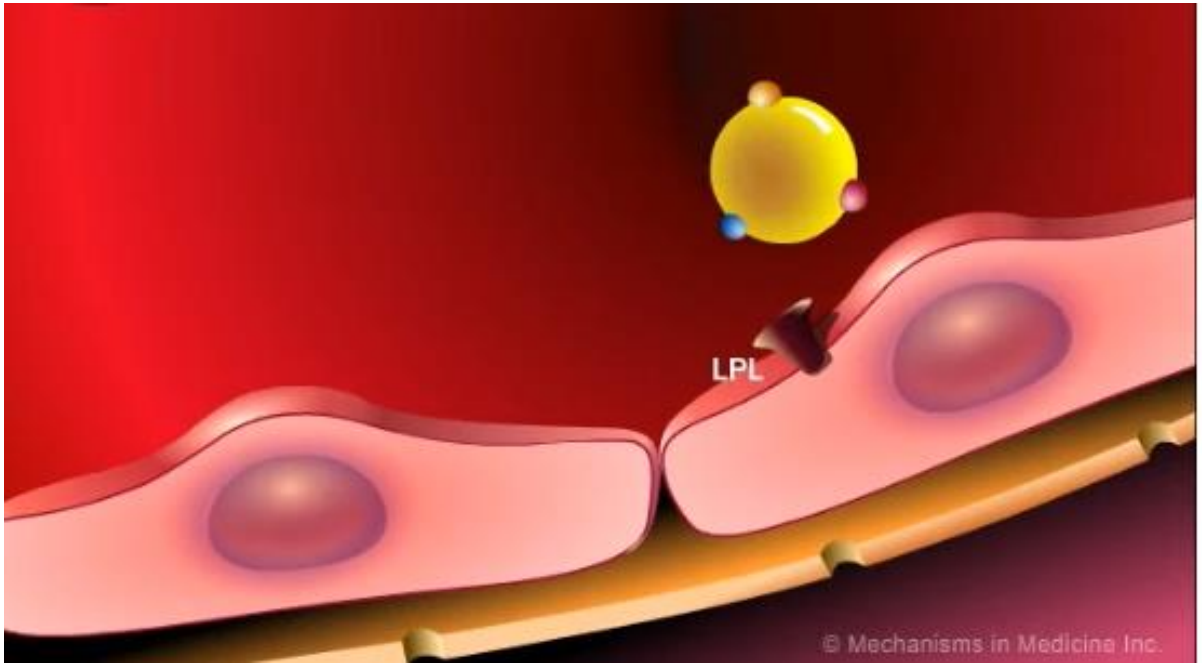
- **Degradation**:

- Apo E present in CM is recognized by hepatic apo E receptor while apo C contains **apo C-II which is activator for lipoprotein lipase (LPL).** This enzyme present extracellular anchored by heparan sulfate to the capillary walls of most tissue, but predominates in adipose tissues, cardiac and skeletal muscles.

- Activated lipoprotein lipase can hydrolyze **triacylglycerol** present in CM to **glycerol** **&** **FFA.**

- Fatty acids are stored by adipose tissues or used for energy by the muscle.

(most of the FFA ,about 90%, are taken upby the extrahepatic tissue where hydrolysis occur. The rest ,about 10%, remains in the circulation bound to albumin & is taken by the liver)


LPL
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- Glycerol is used by liver cells mainly, **due to high activity of glycerol kinase,** for example in lipid synthesis, glycolysis or gluconeogenesis.

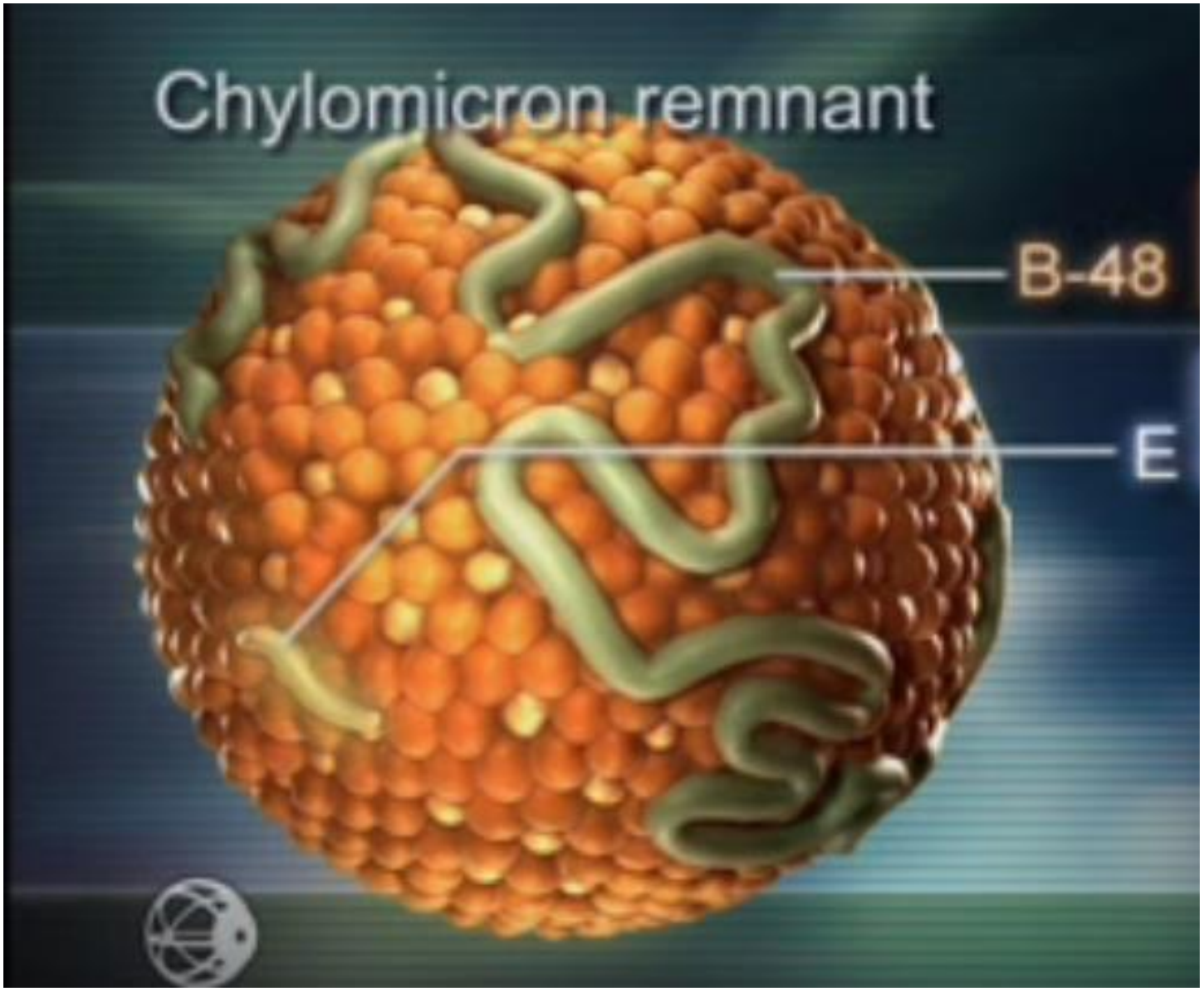
*(All glycerol resulting from hydrolysis of TAG remains in the circulation & is mostly taken up by the liver. It is not taken by other tissues due to the absence of **glycerol kinase enzyme** required for its utilization)*

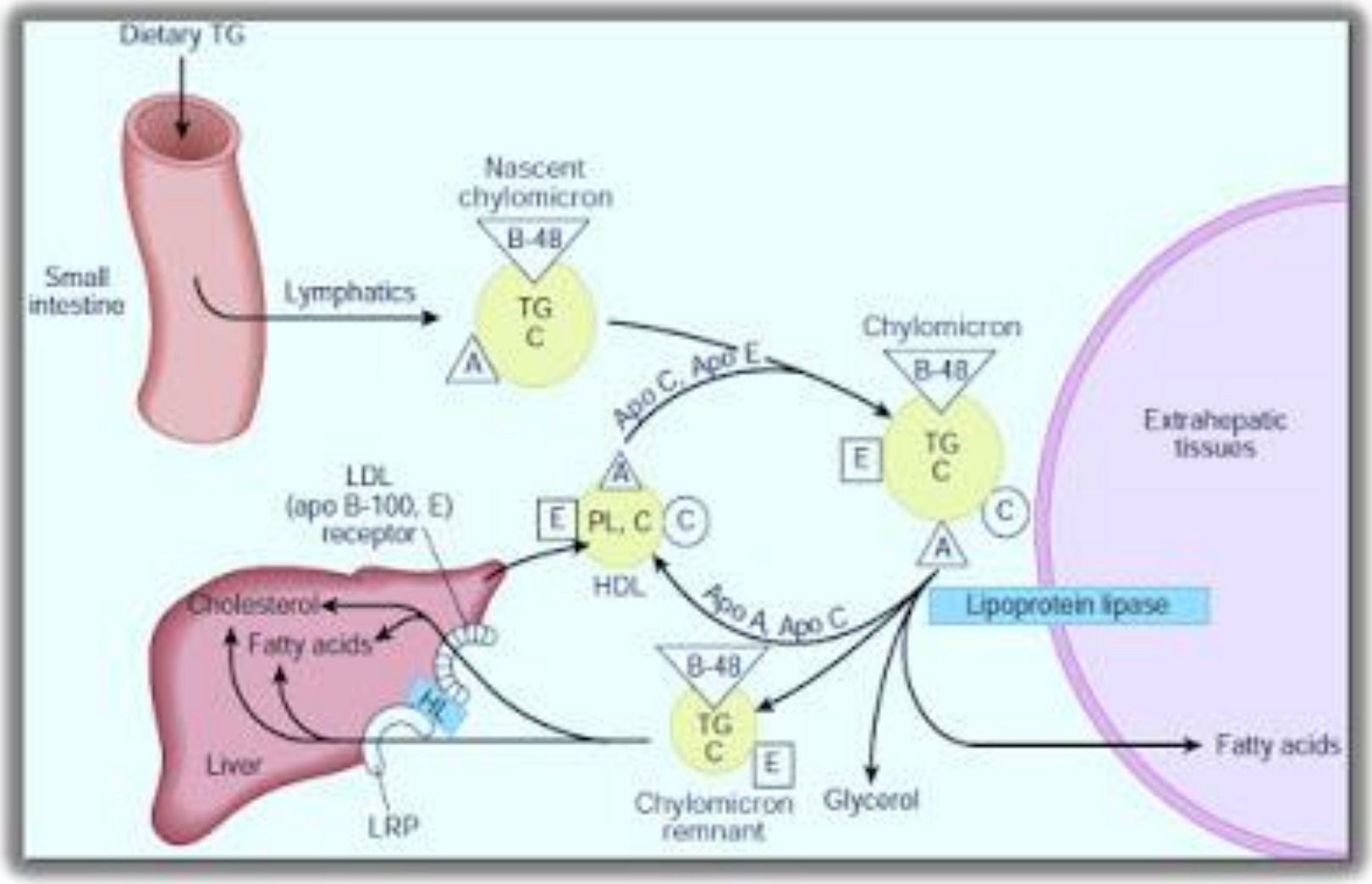
Fate of remnants:

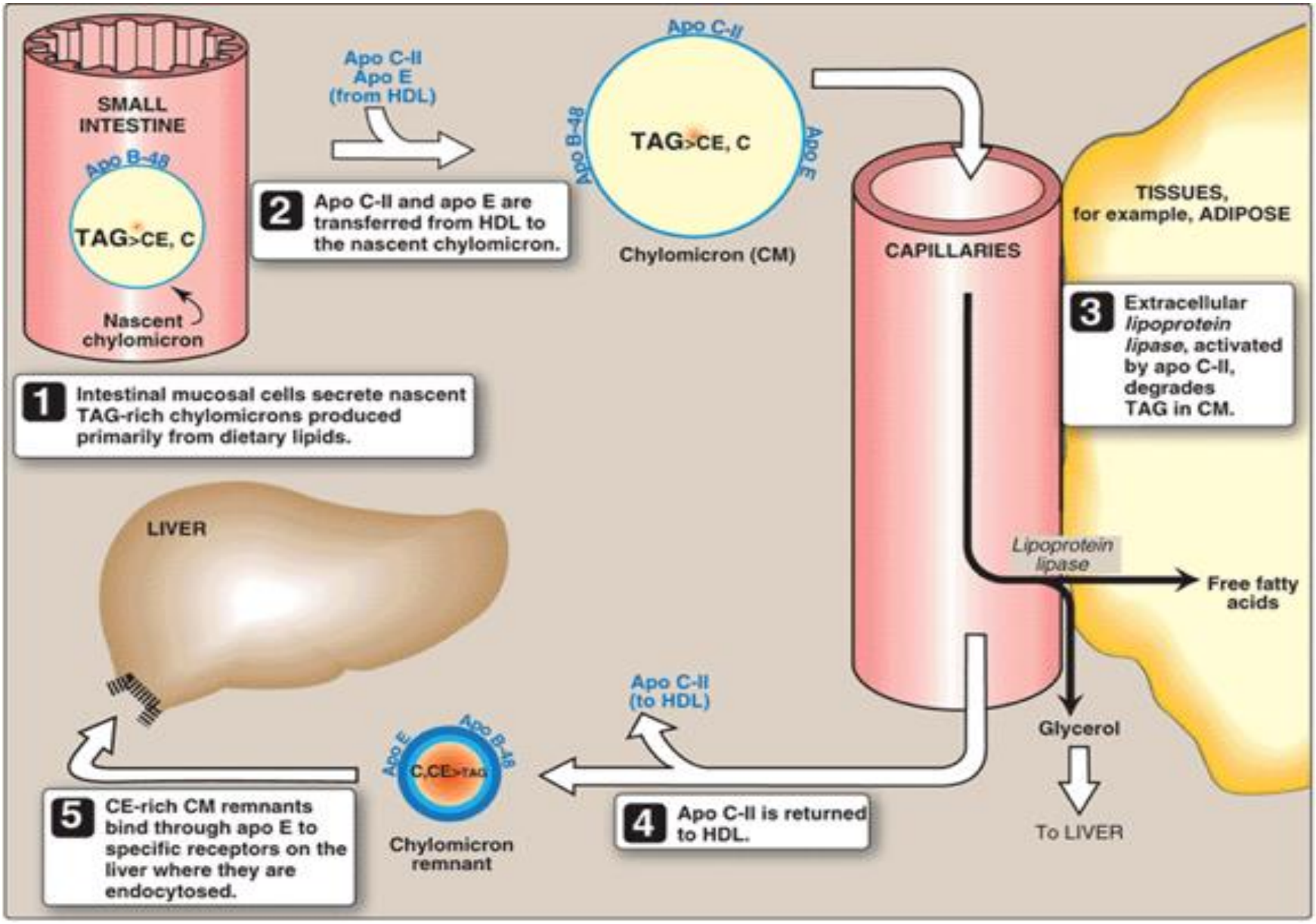
- After triacylglycerol hydrolysis, the remaining part of CM is called **CM remnant** as it decreases in size (they have less percent of TAG and higher percent of C, CE, PL). Hydrolysis of TAG is associated with loss of apo A & apo C to plasma HDL, leaving a CM remnant.

- **Cholesterol ester transfere protein (CETP)** helps transfer of cholesteryl esters from HDL to chylomicron remnants in exchange with TAG. Thus, chylomicron remnants become **very rich in CE and poor in TAG.**
- The CM remnants are taken up by endocytosis by liver cells where their components are hydrolyzed by lysosomes

- The **uptake** is mediated by **specific remnant (Apo E) receptors** & is independent on the amount of C in the liver.


Chylomicron remnant
B-48
E


Dietary TG
Small intestine
Lymphatics
Nascent chylomicron
B-48
TG
C
A
Apo C, Apo E
Chylomicron
B-48
E
TG
C
C
A
Extrahepatic tissues
LDL (apo B-100, E) receptor
E
PL, C
C
A
HDL
Apo A, Apo C
Lipoprotein lipase
Cholesterol
Fatty acids
HL
Liver
LRP
B-48
TG
C
E
Chylomicron remnant
Glycerol
Fatty acids


SMALL INTESTINE
Apo B-48
TAG>CE, C
Nascent chylomicron
Apo C-II
Apo E
(from HDL)
2 Apo C-II and apo E are transferred from HDL to the nascent chylomicron.
Apo C-II
Apo B-48
TAG>CE, C
Apo E
Chylomicron (CM)
CAPILLARIES
TISSUES, for example, ADIPOSE
3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TAG in CM.
1 Intestinal mucosal cells secrete nascent TAG-rich chylomicrons produced primarily from dietary lipids.
LIVER
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
Apo C-II
(to HDL)
Apo E
Apo B-48
C,CE>TAG
Chylomicron remnant
4 Apo C-II is returned to HDL.
5 CE-rich CM remnants bind through apo E to specific receptors on the liver where they are endocytosed.

Metabolism of (VLDL)

- **Origin:** The assembly of VLDL occurs in liver and is called "Nascent VLDL".

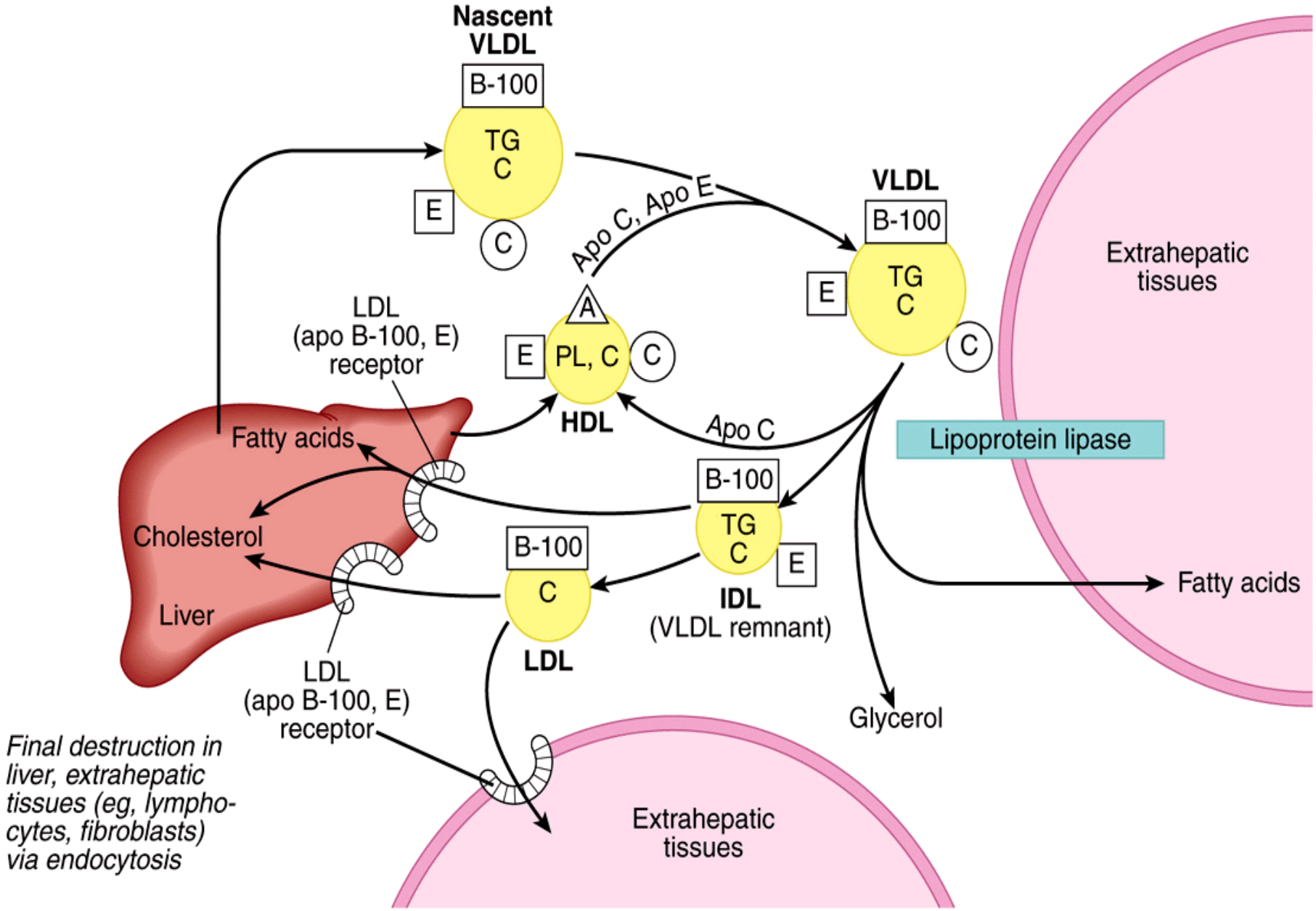
- **Structure &function:** VLDL carries triacylglycerols of endogenous origin to the peripheral tissues.
- The main protein of nascent VLDL is **apo B-100**
- After release of nascent VLDL into the circulation, apo C-II & apo E are transferred from HDL to it.

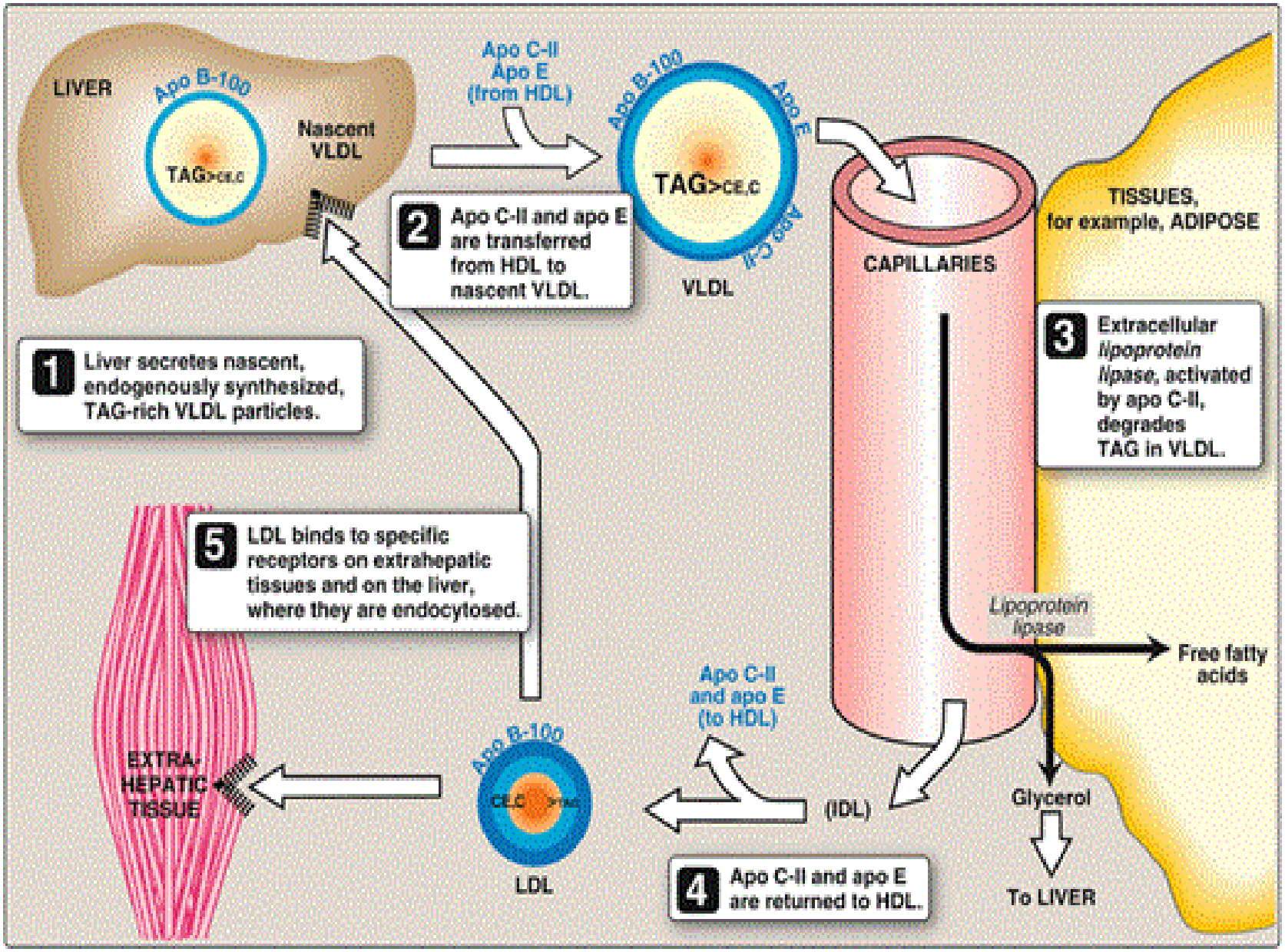
Degradation:

- About 50% of the TAG in VLDL are hydrolized by LPL. This is associated with loss of apo C, which goes to HDL.
- **CETP** helps transfer of CE from HDL to VLDL in exchange with TAG.
- This results in the formation of a lipoprotein particle containing less TAG, more CE, and only proteins apo B-100 and apo E. It is called **intermediate density lipoprotein (IDL),** also known as **VLDL remnant.**

Fate of remnants:

- Most of IDL undergoes further catabolism by **hepatic lipase**, which hydrolyzes most of its TAG, a process associated with loss of apoE to HDL. CETP helps transfer of CE from HDL to IDL in exchange with TAG.
- This results in the formation of a lipoprotein particle poor in TAG, very rich in CE, and containing mainly the protein apo B-100, called **LDL**


Nascent VLDL
B-100
TG
C
E
C
Apo C, Apo E
VLDL
B-100
TG
C
E
C
Extrahepatic tissues
LDL (apo B-100, E) receptor
A
E
PL, C
C
HDL
Apo C
Lipoprotein lipase
Fatty acids
Cholesterol
Liver
B-100
TG
C
E
IDL
(VLDL remnant)
B-100
C
LDL
Fatty acids
LDL (apo B-100, E) receptor
Glycerol
Final destruction in liver, extrahepatic tissues (eg, lympho-cytes, fibroblasts) via endocytosis
Extrahepatic tissues


LIVER
Apo B-100
TAG>CE,C
Nascent VLDL
Apo C-II
Apo E
(from HDL)
Apo B-100
Apo E
TAG>CE,C
Apo C-II
VLDL
CAPILLARIES
TISSUES, for example, ADIPOSE
1 Liver secretes nascent, endogenously synthesized, TAG-rich VLDL particles.
2 Apo C-II and apo E are transferred from HDL to nascent VLDL.
3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TAG in VLDL.
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
(IDL)
Apo C-II and apo E (to HDL)
4 Apo C-II and apo E are returned to HDL.
Apo B-100
CE,C
LDL
5 LDL binds to specific receptors on extrahepatic tissues and on the liver, where they are endocytosed.
EXTRA-HEPATIC TISSUE

Metabolism of LDL

- LDL is formed from VLDL as described before. It may also be directly formed by the liver. Its main function is to transport C, synthesized by the liver, to other tissues.
- The main protein of LDL is **apo B-100**, and the main lipid is **CE.**
- LDL bind to specific **apo B-100** receptors, in both extrahepatic tissues (30%) and liver (70%) where they are endocytosed and metabolized by lysosomes, liberating free C.

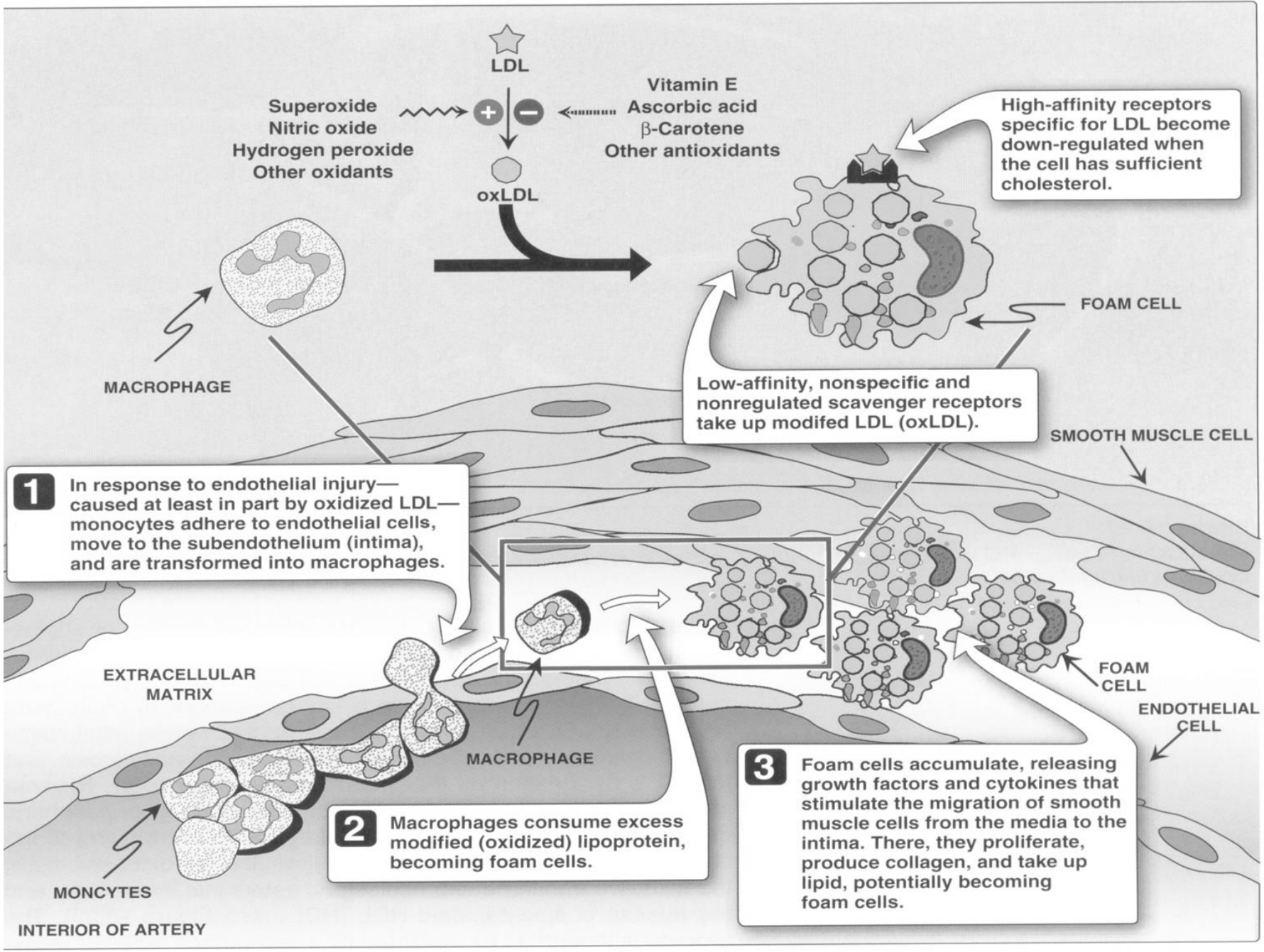
- **The liberated C:**

- decreases the synthesis of C (by inhibiting the enzyme HMG-CoA reductase),
- increases the esterification of C (helping its storage, by increasing the activity of the enzyme **acyl-CoA : C acyltransferase**),
- Downregulates the LDL receptor (to decrease LDL uptake by the cell).

- ***Deficiency of these receptors lead to type II hyperlipoproteinemia, a very sever type of hypercholestrolemia.***

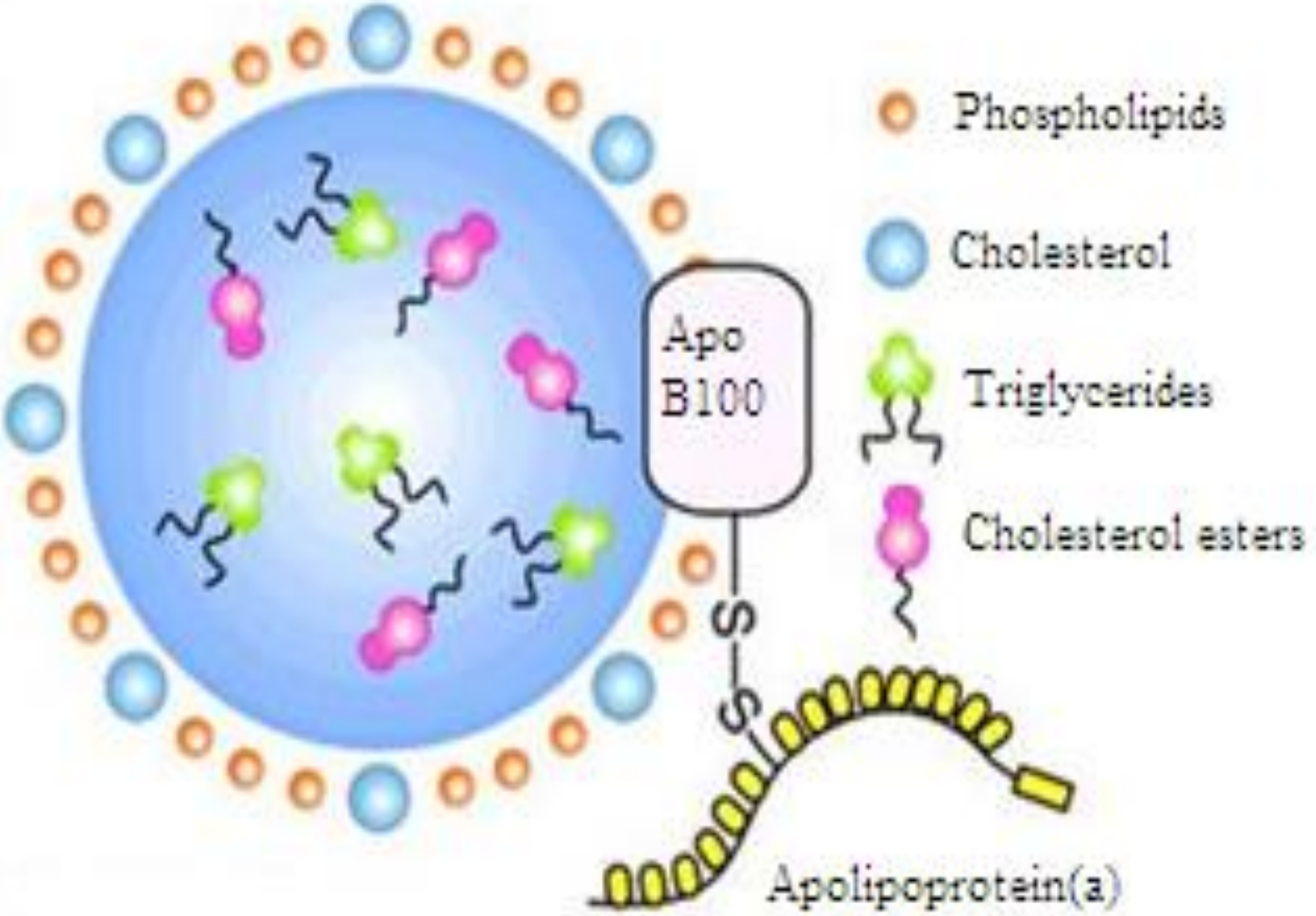
- The above mechanism is responsible for the uptake of most of the plasma LDL.
- Some LDL is also taken by the **macrophages** and arterial smooth muscles by a non-receptor , or a receptor called scavenger receptor, mediated mechanism.
- This pathway becomes more significant if plasma LDL level is **elevated** or if LDL is **modified**.
- Modification of LDL may occur as a result of peroxidation of FA or glycation of proteins(as in diabetes mellitus).

- **Uptake by this mechanism does not regulate C synthesis by the cells.** The macrophages become overloaded with C and are transformed into foam cells. These cells die under the intima of arteries, causing deposition of CE, leading to atherosclerosis.
- Accumulated foam cells in arterial walls also stimulate release of growth factors and proliferation of smooth muscles and formation of plaque (atheroma). These produce narrowing of blood vessels and predispose to thrombosis.
- The incidence of cronary atherosclerosis is directly related to the concentration of LDL in the blood plasma.
- Antioxidants like vitamin C and E decrease the incidence of atherosclerosis .


LDL
Superoxide
Nitric oxide
Hydrogen peroxide
Other oxidants
Vitamin E
Ascorbic acid
β-Carotene
Other antioxidants
oxLDL
High-affinity receptors specific for LDL become down-regulated when the cell has sufficient cholesterol.
FOAM CELL
MACROPHAGE
Low-affinity, nonspecific and nonregulated scavenger receptors take up modifed LDL (oxLDL).
SMOOTH MUSCLE CELL
1 In response to endothelial injury—caused at least in part by oxidized LDL—monocytes adhere to endothelial cells, move to the subendothelium (intima), and are transformed into macrophages.
EXTRACELLULAR MATRIX
FOAM CELL
ENDOTHELIAL CELL
MACROPHAGE
2 Macrophages consume excess modified (oxidized) lipoprotein, becoming foam cells.
3 Foam cells accumulate, releasing growth factors and cytokines that stimulate the migration of smooth muscle cells from the media to the intima. There, they proliferate, produce collagen, and take up lipid, potentially becoming foam cells.
MONCYTES
INTERIOR OF ARTERY

Role of lipoprotein (a) in heart disease:

- Lipoprotein (a), or lp(a), is a particle that when present in large quantities in the plasma, is associated with an increased risk of cronary heart disease.
- Lipoprotein (a) is nearly identical in structure to an LDL particle. Its distinguishing feature is the presence of an additional apolipoprotein molecule, apo (a), that is covalently linked at a single site to apo B 100.


Phospholipids
Cholesterol
Triglycerides
Cholesterol esters
Apo
B100
S
S
Apolipoprotein(a)

- LP (a) plasma levels are determined by genetic factors. However, factors as diet may play some role as trans fatty acids have been shown to increase LP (a) and estrogen decrease both LDL & LP (a).
- Apo (a) is a highly homologous to plasminogen, the precursor of blood protease (plasmin) which causes fibrinolysis.
- It is hypothesized that elevated LP (a) slows the breakdown of blood clots that trigger heart attacks because it competes with plasminogen for the binding of plasminogen activators.

Metabolism of (HDL)

- They are formed by liver cells and small intestine as discoidal HDL which are mainly formed of **PL** bilayer, **free C**, and apolipoproteins (A,C,D,E) then accept free C from extrahepatic tissues, where it is esterified by **LCAT** (**This enzyme is secreted by the liver and binds to HDL and is activated by apo A-I present in HDL**).

- LCAT catalyzes the transfer of acyl group from position 2 of lecithin to C to form CE and lysolecithin.

- CE form a central hydrophobic core that pushes the PL bilayer apart and converts the discoidal HDL into the spherical **HDL_3**.

- HDL_3 also receives excess surface lipids, C, PL from CM and VLDL when broken by LPL enzyme. HDL_3 now becomes **HDL_2**.

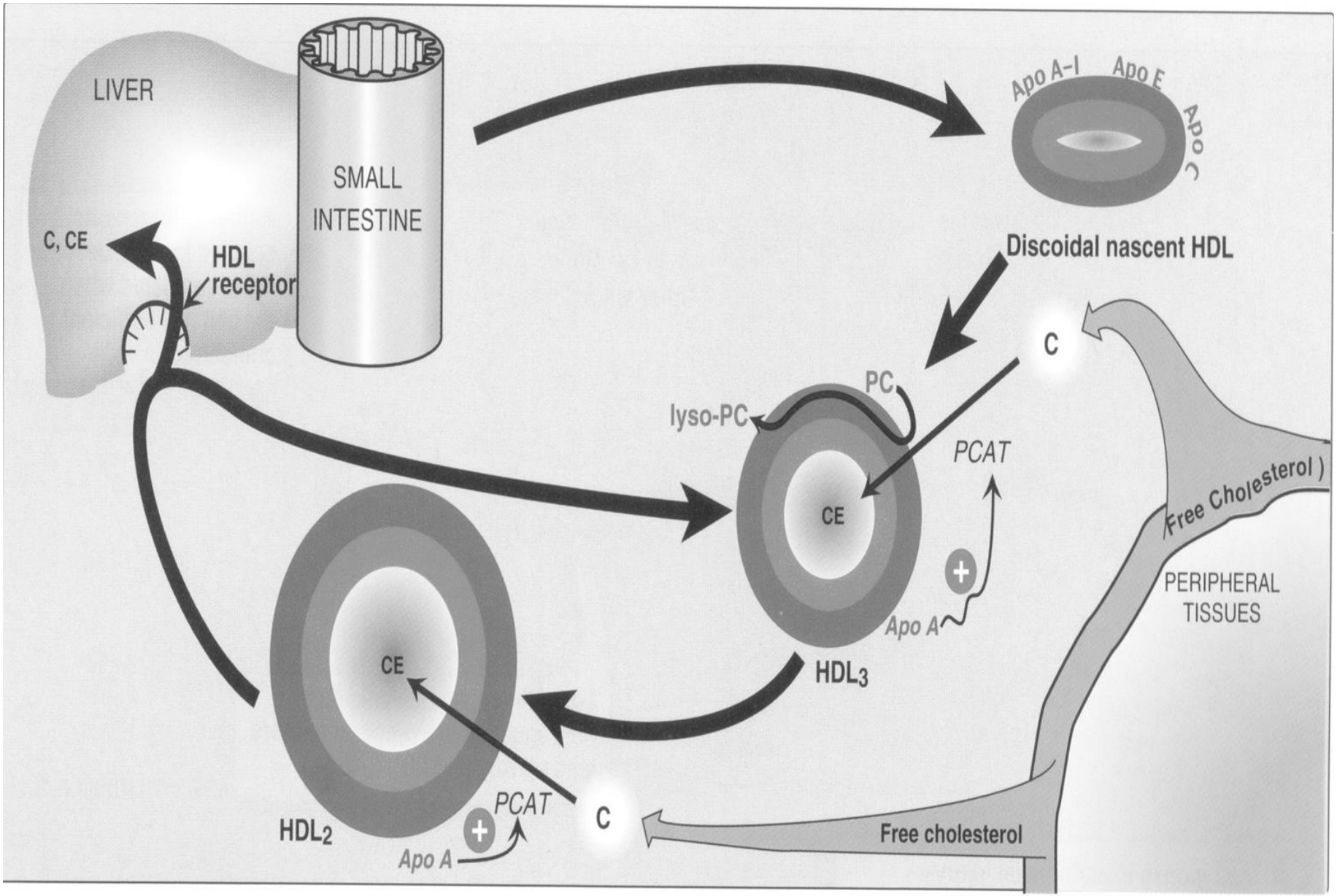
- ***Hepatic lipase*** hydrolyzes and removes part of the TAG, CE, PL from HDL_2 reforming HDL_3 .

- HDL act as reservoir for different apoproteins (C,E), which are important for metabolism of CM and VLDL.

- HDL by the mean of CETP (apo D) provide CE to CM remnants and LDL in exchange with TAG.

- HDL are endocytosed by liver cells, where CE are hydrolyzed. The free C released is either repacked into lipoproteins or converted to bile acids to be secreted in bile.

- So, HDL are important for removal of C from tissues to the liver **(reverse C transport)** and high levels of HDL protect against atherosclerosis.


LIVER
SMALL INTESTINE
C, CE
HDL receptor
Apo A-I
Apo E
Apo C
Discoidal nascent HDL
C
PC
lyso-PC
PCAT
CE
Apo A
HDL3
CE
HDL2
PCAT
Apo A
C
Free cholesterol
Free Cholesterol)
PERIPHERAL TISSUES

❖Notes:

- **While some components of the Lipid Profile (Total Cholesterol and HDL Cholesterol) are not impacted by food, others, particularly the triglyceride level, can be.**
- **The LDL cholesterol is a value often obtained by a calculated method that relies on the accurate measurement of triglycerides. For this reason, a non-fasting sample can raise triglycerides and yield an inaccurate LDL cholesterol calculation.**

- **There is no simple, direct way to measure VLDL cholesterol. VLDL cholesterol is usually estimated as a percentage of your triglyceride value.**
- **LDL cholesterol (mg/dL) = total cholesterol – HDL cholesterol – (triglycerides/5)**
- **where “triglycerides/5” is used to represent very low density lipoprotein-C (VLDL-C).**

- **Non-HDL cholesterol, another calculated measure, does not rely on triglycerides, however, and can be done as a non-fasting sample. Furthermore, the non-HDL cholesterol value reflects all of the major lipoproteins linked with a higher risk of cardiovascular disease.**
- **Some lipid experts argue that the non-HDL cholesterol value is better than the LDL cholesterol value for predicting heart disease.**
- **Your non-HDL cholesterol result refers to your total cholesterol value minus your HDL cholesterol.**

- **For these reasons, if one desires an accurate triglyceride and calculated LDL cholesterol level, it is ideal to fast for 8-12 hours prior to the test. However, if this is not the case, total cholesterol, HDL cholesterol and non-HDL cholesterol values may still be obtained accurately, and will be useful.**

- **Studies indicate that the risk for atherosclerosis is more related to the number of LDL particles (LDL-P) than the total amount of cholesterol within these particles.**
- **Traditional lipid testing measures the amount of LDL cholesterol (LDL-C) present in the blood, but it does not evaluate the number of particles of LDL (LDL-P).**
- **It is also important to remember that LDL particles carry other molecules than cholesterol. For example, triglycerides (TG) are also carried within LDL-particles. TG molecules are larger than cholesterol ester molecules.**

- **If the number of TG molecules in an LDL-particle is high, there will be less space for cholesterol molecules. Therefore, if triglycerides are high, it may take many more LDL particles to carry a given amount of cholesterol.**
- **Therefore high LDL particle count may be associated with small, cholesterol depleted, triglyceride rich particles.**
- **Research has shown that high levels of triglycerides are associated with small LDL particle size.** ***(There is an inverse correlation between blood levels of triglycerides and LDL particle size. Thus, the higher your triglycerides, the greater the number of small LDL particles. Conversely, the lower your triglycerides, the higher the number of large, fluffy LDL particles)***

- **Now, what does all this mean? It means that one person (person A) may have large cholesterol rich LDL particles, while another (person B) may have smaller cholesterol depleted particles. These two persons may have the same LDL-C concentration. However, person B will have higher LDL particle number (LDL-P).**
- ***Despite similar levels of LDL-C, person B is at higher risk for future cardiovascular events. Furthermore, person B will have more small LDL-particles.***

Hyperlipoproteinemias

- **Type I (Hyperchylomicronemia):**

- The familial type is due to *deficiency of lipoprotein lipase* **or** *deficiency of apo CII*
- Increased plasma levels of chylomicrons and VLDL
- Increased plasma level of triacylglycerols and slight increase in plasma cholesterol.
- So, the plasma is turbid.

- **Type II (Hyperbetalipoproteinemia):**

-The familial type is due to defective LDL receptor **or** mutation in ligand region of apo B-100.

-The acquired type occurs in hypothyroidism as T3 increases the sensitivity of LDL receptor to LDL.

- There are two subtypes of hyperbetalipoproteinemia:

1) **Type IIa:** It is characterized by increased plasma LDL **without** increase in VLDL. So, the plasma is clear.

2) **Type IIb:** It is characterized by increased plasma LDL **with** a slight increase in plasma VLDL. So, the plasma is slightly turbid.

There is marked hypercholesterolemia which if familial called **familial hyper cholesterolemia**. Also, there is a slight increase in plasma triglycerides levels, especially in type IIb.

Atherosclerosis & coronary heart disease were sequelae of elevated LDL & hypercholesterolemia.

- **Type III (Dysbetalipoproteinemia):**

-The familial type is due to abnormality in apo E leading to the defective uptake of chylomicrons & VLDL remnants by apo E receptor.

-Increase chylomicron **remnants** & VLDL **remnants** in plasma.

- **Type IV (Hyperprebetalipoproteinemia):**

- It is characterized by increased plasma VLDL & triacylglycerols and some increase in plasma cholesterol.
- **The familial type (famelial hypertriacylglycerolemia)** which is ***the most common familial lipid abnormality*** is often associated with hyperinsulinemia and poor glucose tolerence

-The acquired type is due to type II diabetes mellitus, obesity, alcoholism and administration of progestational hormones.

- **Type V**

(Hyperchylomicronemia & Hyperprebetalipoproteinemia):

The cause is unknown

- **Type VI (Hyperalphalipoproteinemia):**

-It is due to familial increase in HDL concentration.

-It occurs during estrogen therapy.

-There is reduced risk of atherosclerosis.