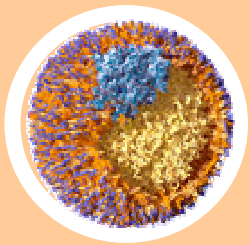
Cellular Biochemistry [918SM]



Module 2_3

Intercellular Lipid Transport

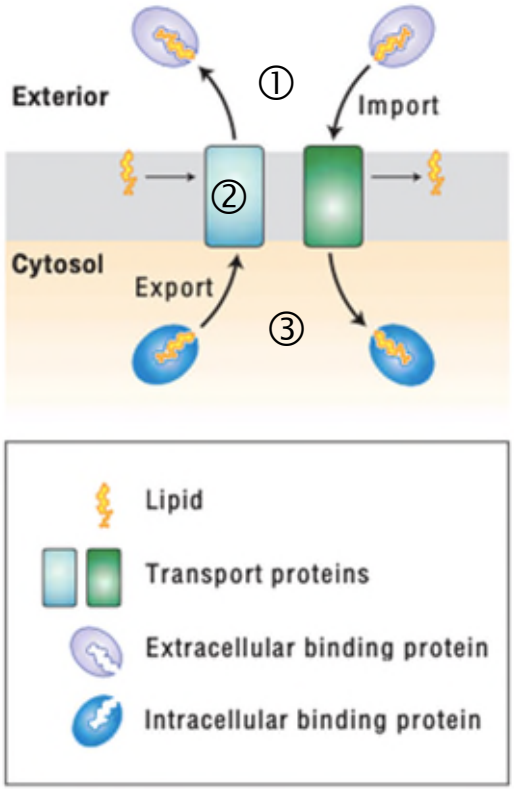
A. Tossi atossi@units.it

AA 2026-2027

LIPID TRANSPORT IN AND OUT OF CELLS

Two main routes for the import, export and transport of cellular lipids

1) I/E Mediated by **Transport Proteins**

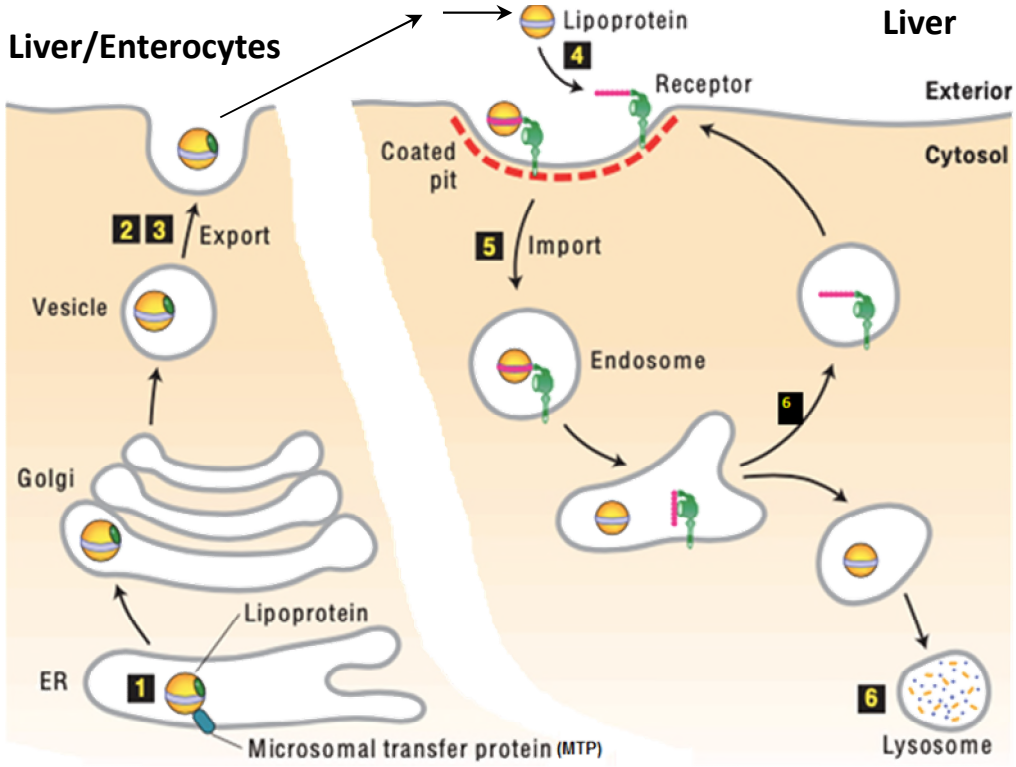


① **eg. Serum albumin, CETP**

② **eg. ABC Transporter**

③ **eg. FABP**

2) **Transport** mediated by **Lipoproteins (LP)**



① **Lipoproteins assembled** in liver/enterocyte ER

② Carried to CP membrane by **Golgi-dependent secretory pathway**

③ **Exocytosis** & **delivery to tissue**

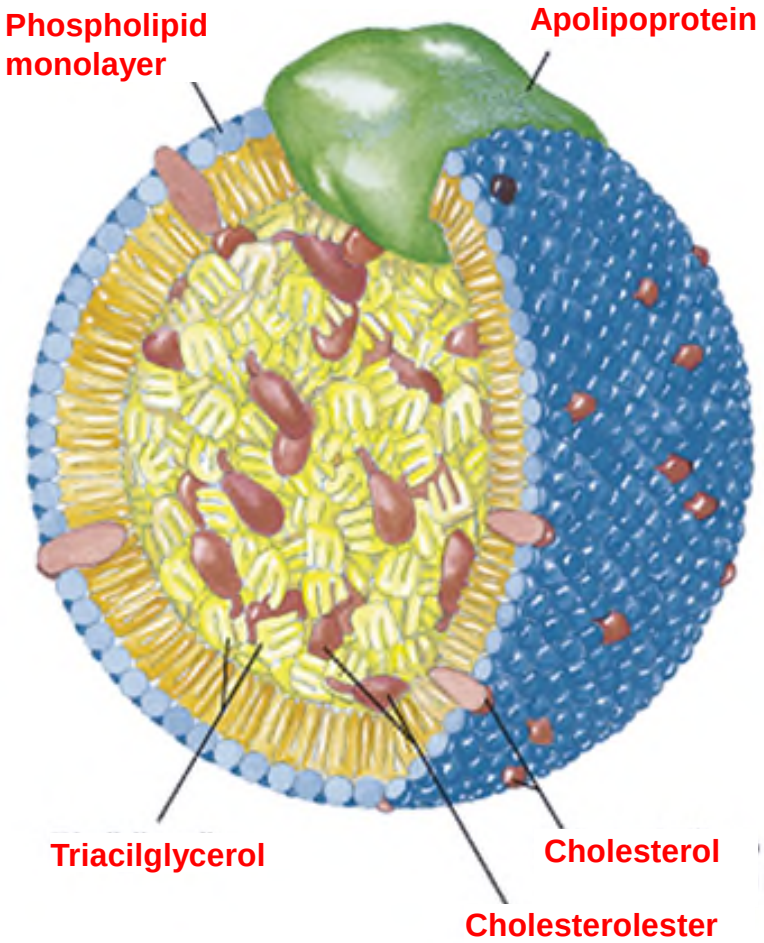
④ **LP remnants** return to liver and **bind to *LP receptors***

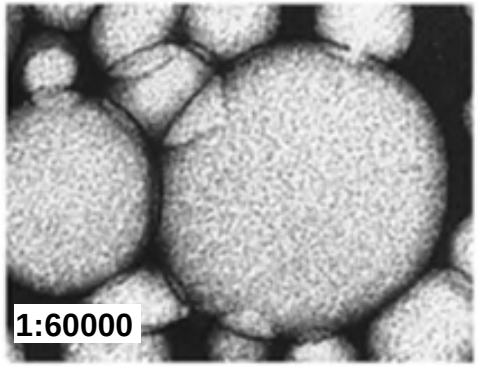
⑤ **Endocytosis → endosomes**

⑥ Delivered to **lysosomes** for dismantling (LP receptor recycled)

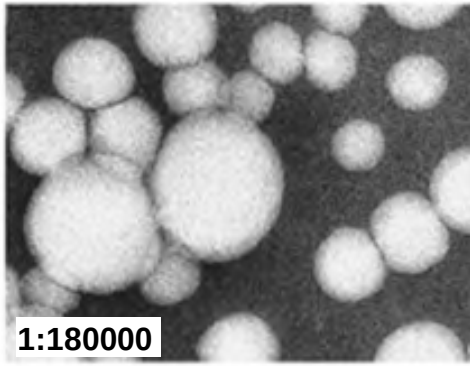
LIPOPROTEINS (LP)

- **Large complexes composed of different lipids and Apolipoproteins**
  - Transport lipids (TAG, CL, CLE, & lipophylic vitamins) in biological fluids (plasma, interstitial fluid, and lymph) in which they are poorly soluble, to and from tissues
  - Each type of LP transports cargo with different destinations and varies in size and density.

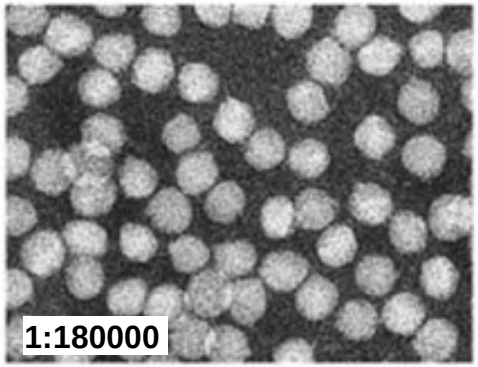




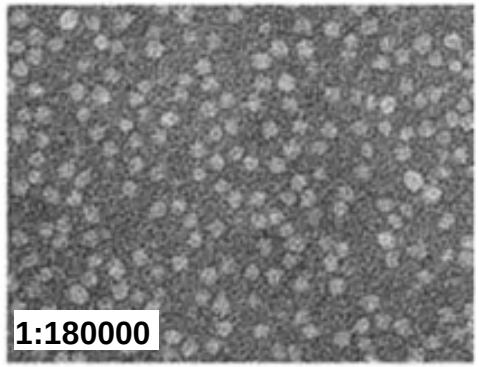
CHYLOMICRON: Largest size, lowest density



VLDL (Very low density LP)
Large size, low density



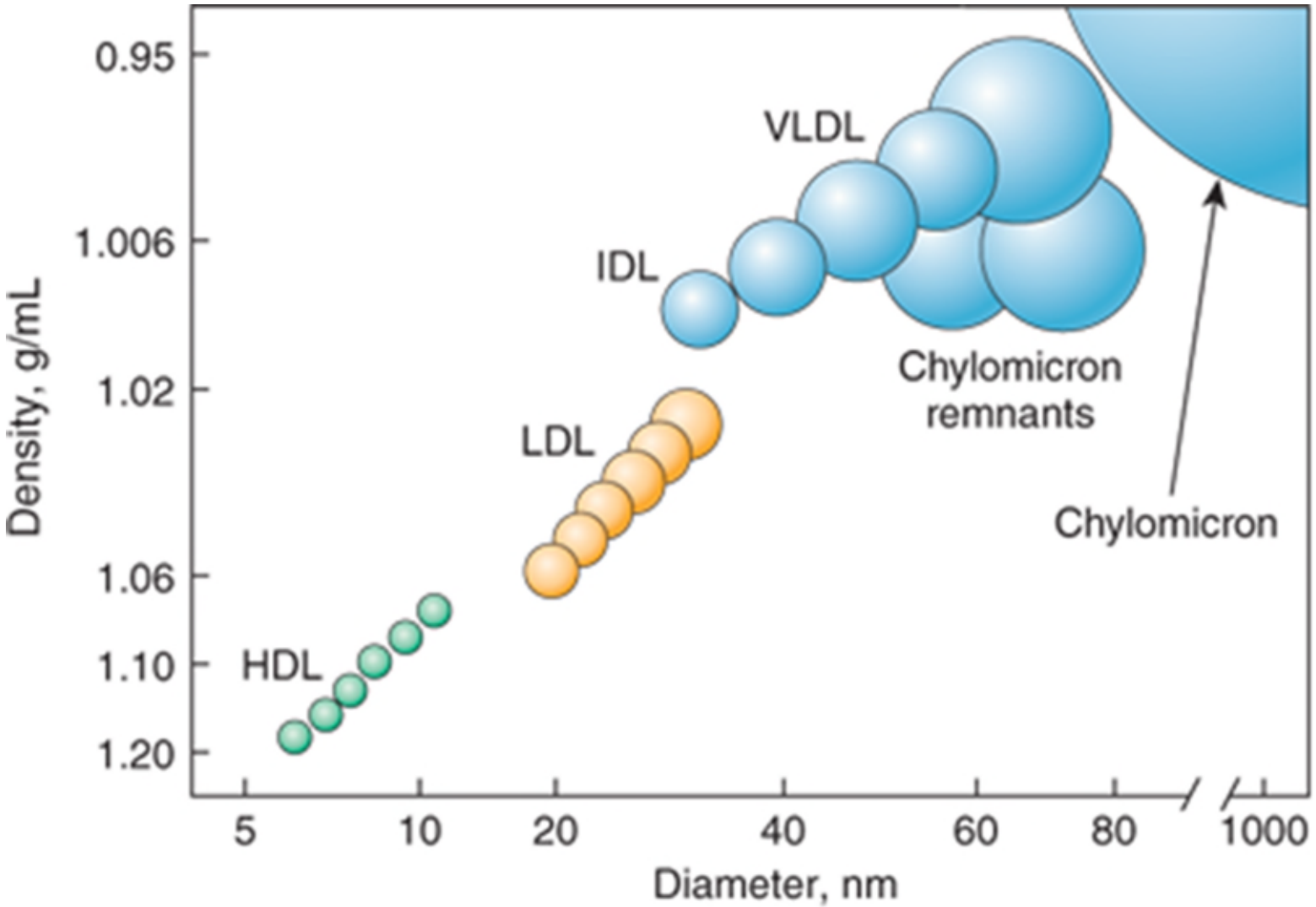
LDL (Low density LP)
Small size, increased density



HDL (High density LP)
Smallest size, highest density

LIPOPROTEIN SIZE AND DENSITY

- **Lipoprotein density is inversely proportional to their size**
  - Proteins are denser than lipids

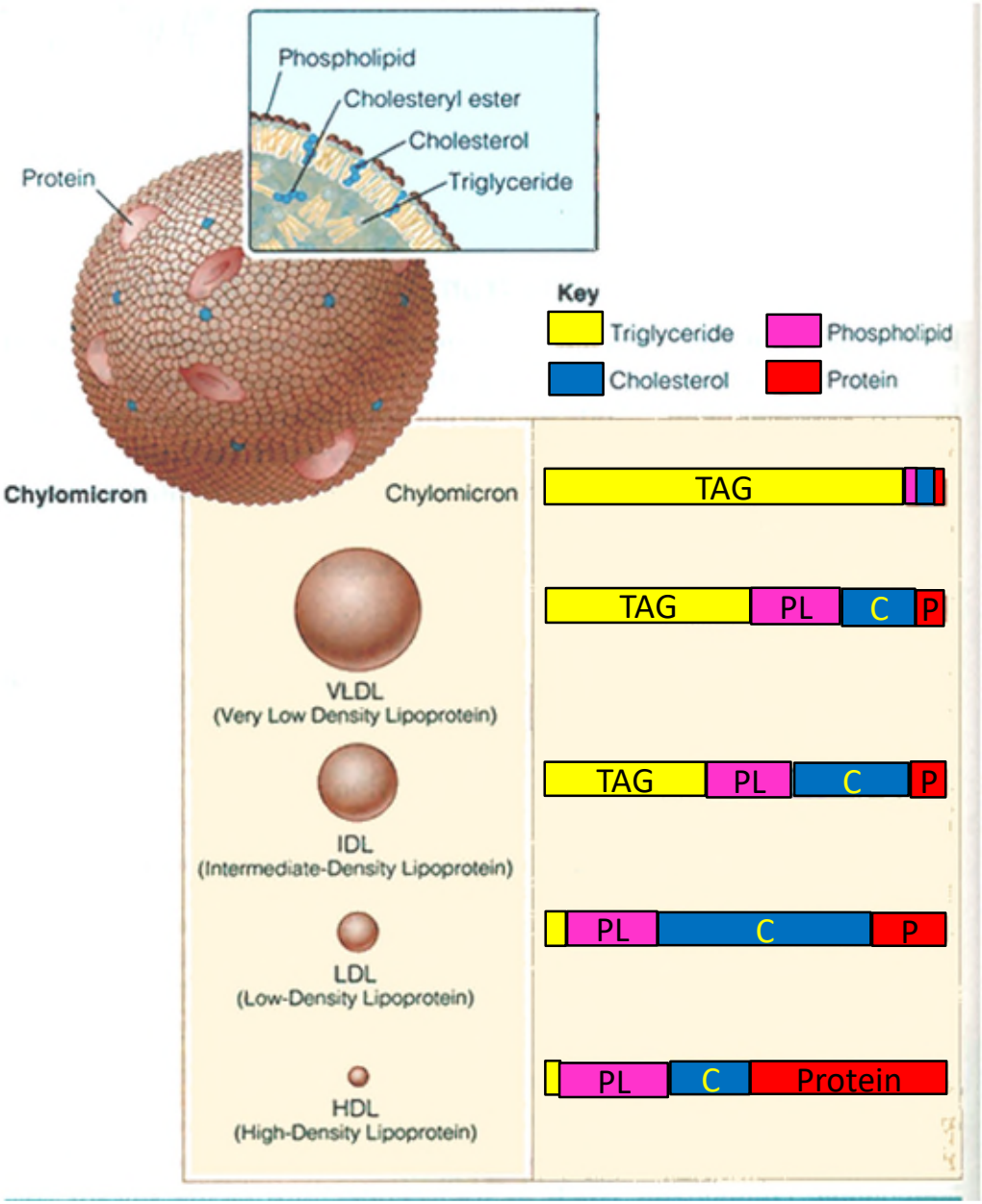


LIPOPROTEIN COMPOSITION, ORIGIN, CARGO & DESTINATIONS

Composition of lipoproteins in human plasma

	Chylomicrons	VLDL	LDL	HDL
Origin	Intestine	Liver	Liver	Tissues
Destination	Tissues	Tissues	Tissues	Liver
Size (nm)	~500	~60	~25	~ 10
Density (g/ml)	~0.95	~1.0	~1.05	~1.15
Apoliporoteins	B_{48}, C, A_{1-5}, E	B_{100}, C, E	B_{100}	A_{1-5}, C, E
composition				
Protein	2%	10%	20%	40%
Lipid	98%	90%	80%	60%
of which				
Triglyceride	**88%**	**56%**	13%	13%
Phospholipid	8%	20%	28%	47%
Free cholesterol	1%	8%	10%	10%
Cholesteryl esters	3%	**16%**	**48%**	**30%**

LIPOPROTEIN COMPOSITION, ORIGIN, CARGO & DESTINATIONS (cont.)



TAG from diet

↓ Bile salts, *Pancreatic lipase*

FA/MAG

enterocytes ↓ *Acyltransferases*

TAG → Chylomicrons

capillaries ↓ *Lipoprotein lipase*

FA/MAG ← **TAG in VLDL** ← ***LIVER***

FA/MAG → **CLE in LDL**

adipocytes/ muscle ↓ *Acyltransferases*

Storage TAGs

adipocytes ↓ *Hormone-sensitive lipase (HSL)*

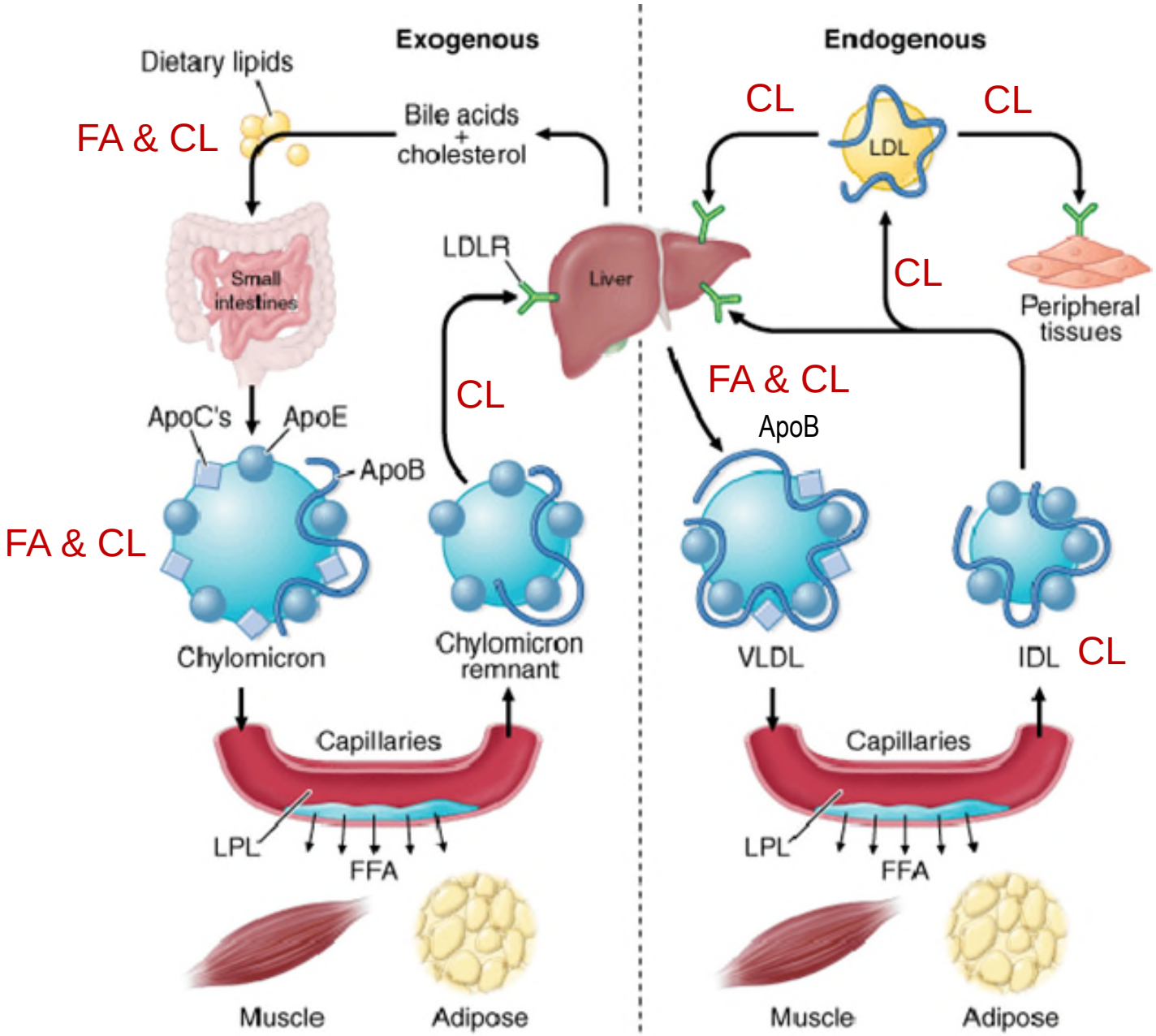
FA → Serum albumin

blood ↓

Tissues (β-ox)

CL in HDL → ***LIVER***

EXOGENOUS AND ENDOGENOUS PATHWAYS FOR LIPOPROTEINS



ROLES OF APOLIPOPROTEINS

ApoA1

- **source:** intestine/liver
- **LP:** **VLDL** and **chylomicrons** (which transfer it to HDL, mediates uptake)
- **Function**: structural protein - Activates *lecithin cholesterol acyltransferase* (CL → CLE)

ApoB48

- **Source:** Intestine
- **LP:** **Chylomicrons**
- **Function:** structural protein - Truncated form of ApoB100 - Does not bind receptors

ApoB100

- **Source:** liver
- **LP:** **VLDL, IDL, LDL**
- **Function:** structural protein – Ligand for LP receptor (LPR) on tissue cells

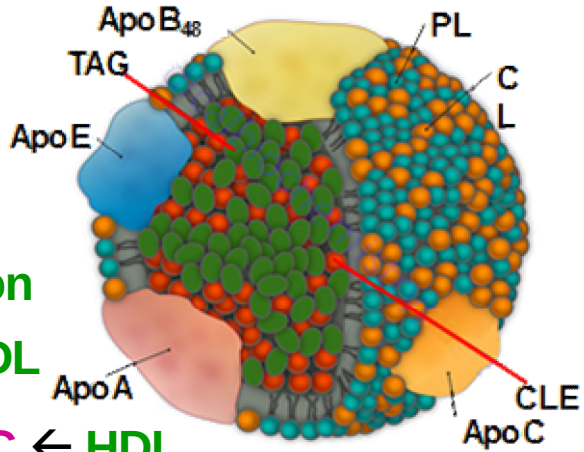
ApoC II

- **Source:** liver
- **LP:** **Chylomicrons, VLDL** and **HDL** (HDL → CM, VLDL, remnants → HDL)
- **Function:** *Lipoprotein lipase* cofactor on capillary endothelial cells – mobilizes FA from LP

ApoE

- **Source:** liver
- **LP:** **Chylomicrons, IDL** and **HDL** (exchange it)
- **Function:** ligand for tissue LP receptor and liver scavenger receptor (for remnants)

LIPOPROTEIN FUNCTIONS - CHYLOMICRONS

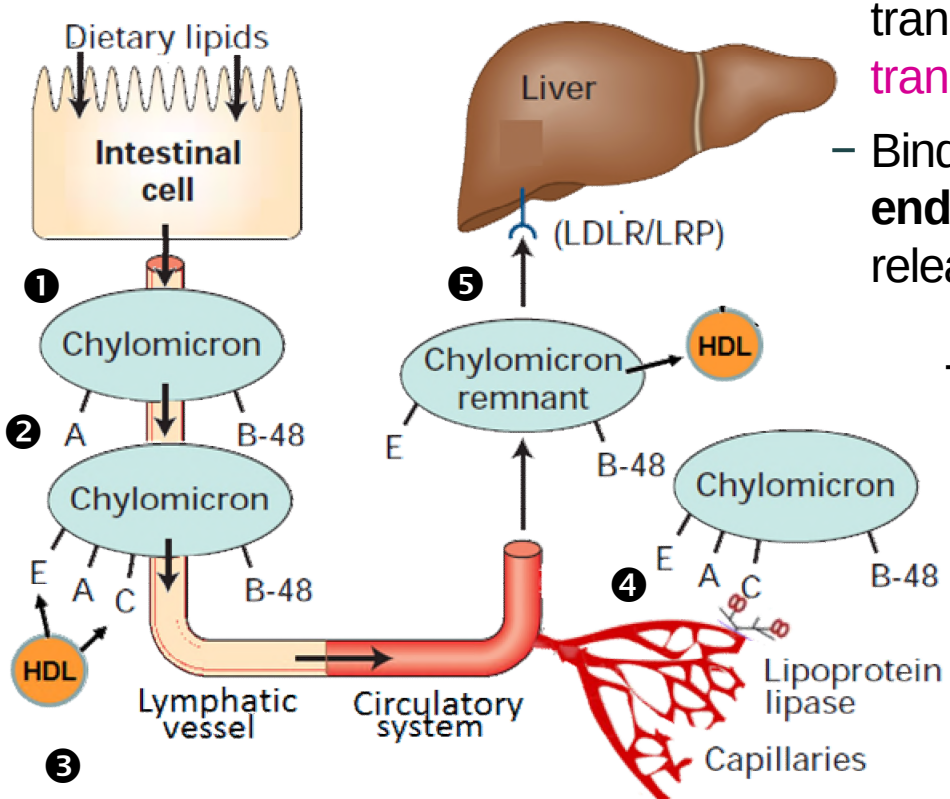


Mature Chylomicron

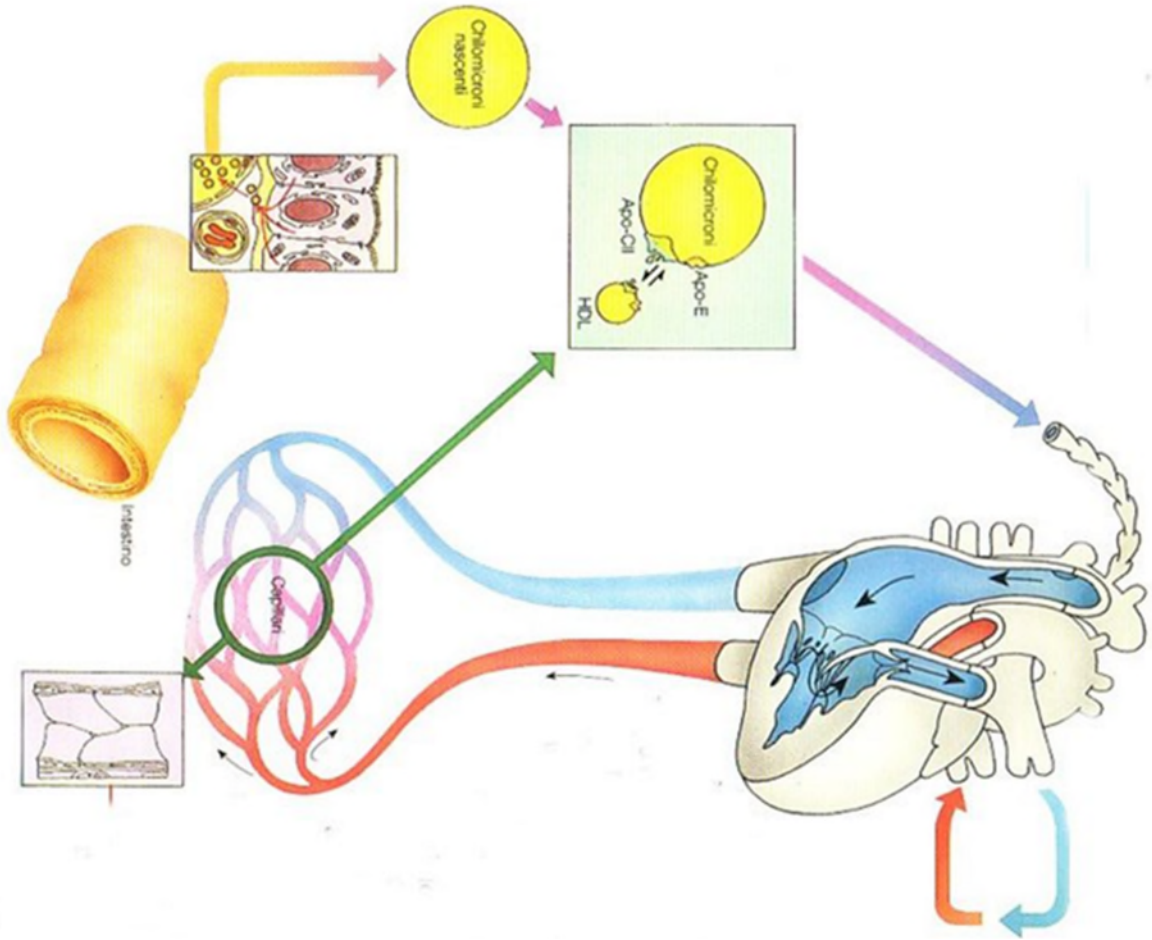
ApoA → HDL

ApeE, ApoC ← HDL

- Formed in the **ER of enterocytes** with the aid of **MTP**, they are secreted in **immature form** including apoproteins **ApoB48** and **Apo A**❶
- Secreted into specialized **lacteal lymphatic capillaries** ❷, reach the thoracic duct, enter the bloodstream via **subclavian vein** to reach tissues
- **During transit** they pass **Apo A** to **HDL**, and receive **ApoE** and **ApoC** from HDL, which also transfer CLE using **CETPs** (cholesterol ester transfer proteins) ❸.
- Bind to ***Lipoprotein lipase*** located on **capillary endothelia** (via **Apo C**) that hydrolyzes TAGs releasing FA/MAG that translocate into the cells ❹
- Remnants return to the liver, returning **Apo C** to HDL, and are internalized into hepatic cells via the LDLR receptors (low density lipoprotein receptor), which recognizes Apo B100, and LRP (LDLR related protein) which recognizes Apo E.❺.



CHYLOMICRON METABOLISM - SUMMARY



Enterocytes → lacteal duct → mesenteric ducts → thoracic duct → subclavian vein → tissues

Immature chylomicrons → ApoC/E from **HDL** → mature chylomicrons → TAG to tissue (***LPL***)

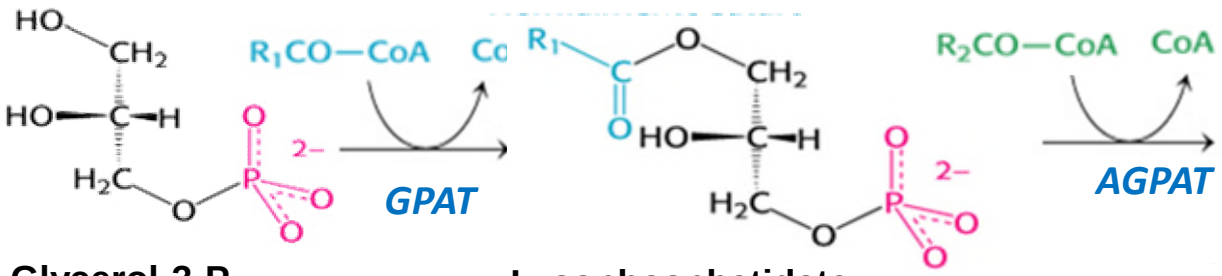
----------Enterocytes---------- lymphatic system-------

---------- Circulatory system ----------↓

----------Epathocytes----------

Recycling ← Receptor mediated endoicytosis ← CLE from **HDL** ← Remnants

TAG RECONSTITUTION IN ADIPOCYTES



Glycerol-3-P

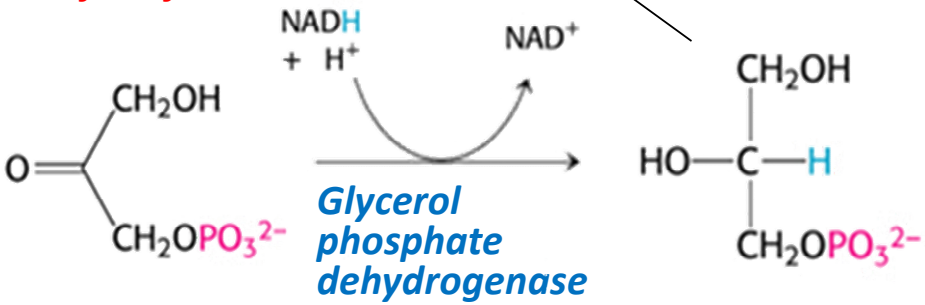
Lysophosphatidate

Phosphatidate

Endoplasmic reticulum

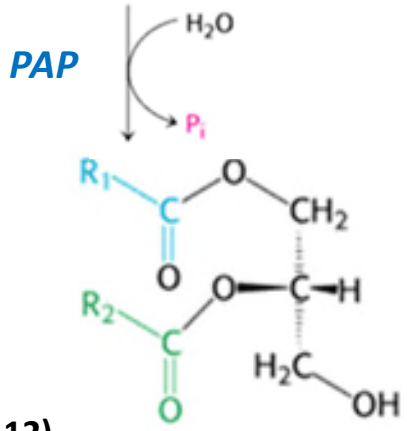
Cytosol

Glycolysis



Dihydroxyacetone-P

Glycerol-3-P



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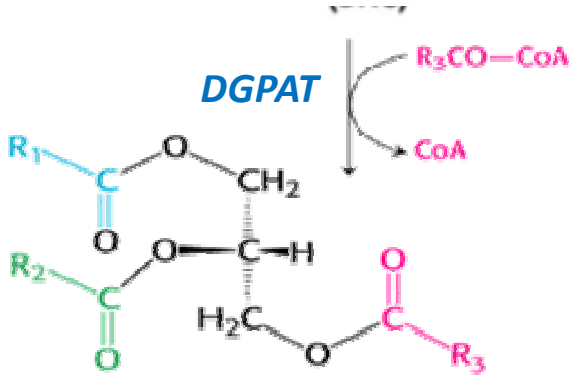
Phospholipids ⇄ DAG

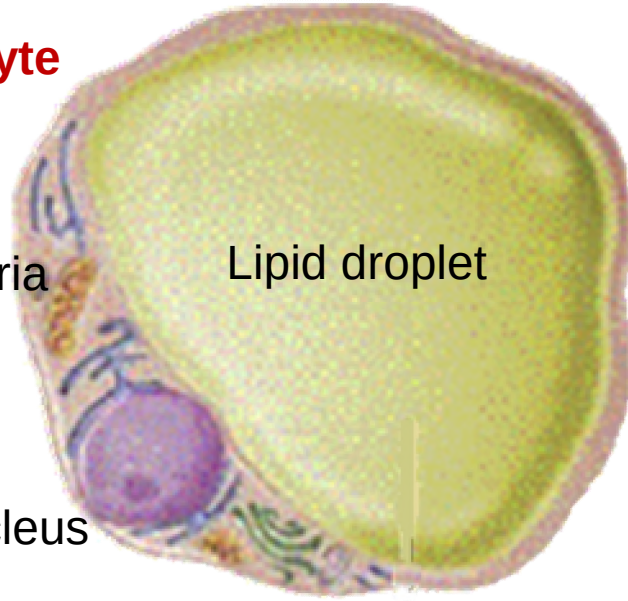


TAG

GPAT = glycerol-3-phoshpate acyltransferase
AGPAT = acylglycerol-3-phoshpate acyltransferase
PAP = phosphatidate phosphatase
DGPAT = diacylglycerol-3-phoshpate acyltransferase

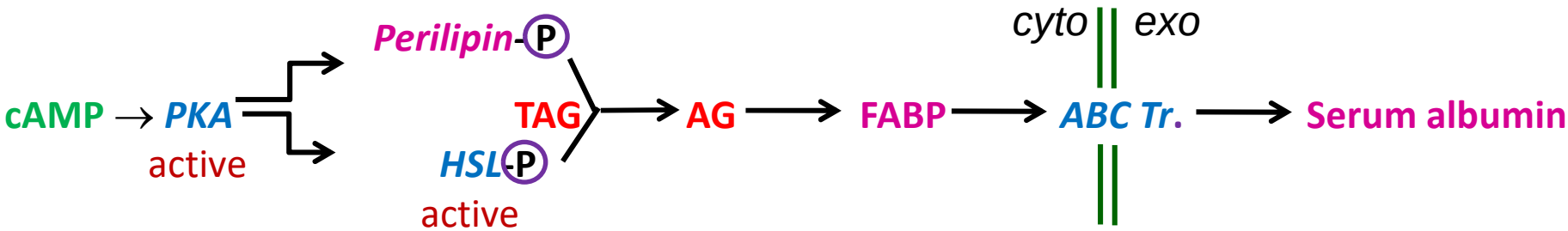
TAG MOBILIZATION FROM ADIPOCYTES

Function of adipocytes



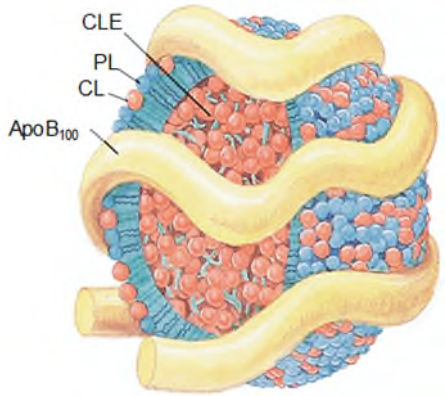
- To **store fat** in an **easily metabolizable form**
  (TAG contribute up to 90 % of weight)
- To **release FA** in a **controlled manner**
  (Have receptors for:
  Glucagon & cathecholaminee (**GPCR**, $G_{\alpha s}$ → ***PKA***)
  Insulin (**RPTK**, → ***PPP1***)
- TAGs are stored in adipocytes as lipid droplets with a core composed of CLE and TAG, surrounded by a layer of phospholipids (PL).
- Embedded in droplet surface are **Perilipins**, which when phosphorylated by ***PKA*** attach ***Hormone sensitive lipase*** (***HSL***, also activated by ***PKA*** phosphorylation)
- This mobilizes stored TAG, releasing glycerol & FA that are exported, binding serum albumin

- **Glucagone/epinefrina** (insufficient glucose) → **cAMP** transduction cascade

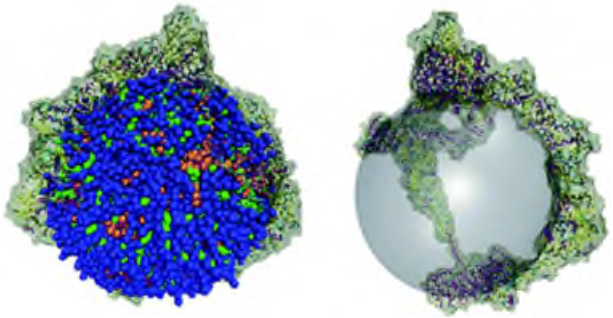


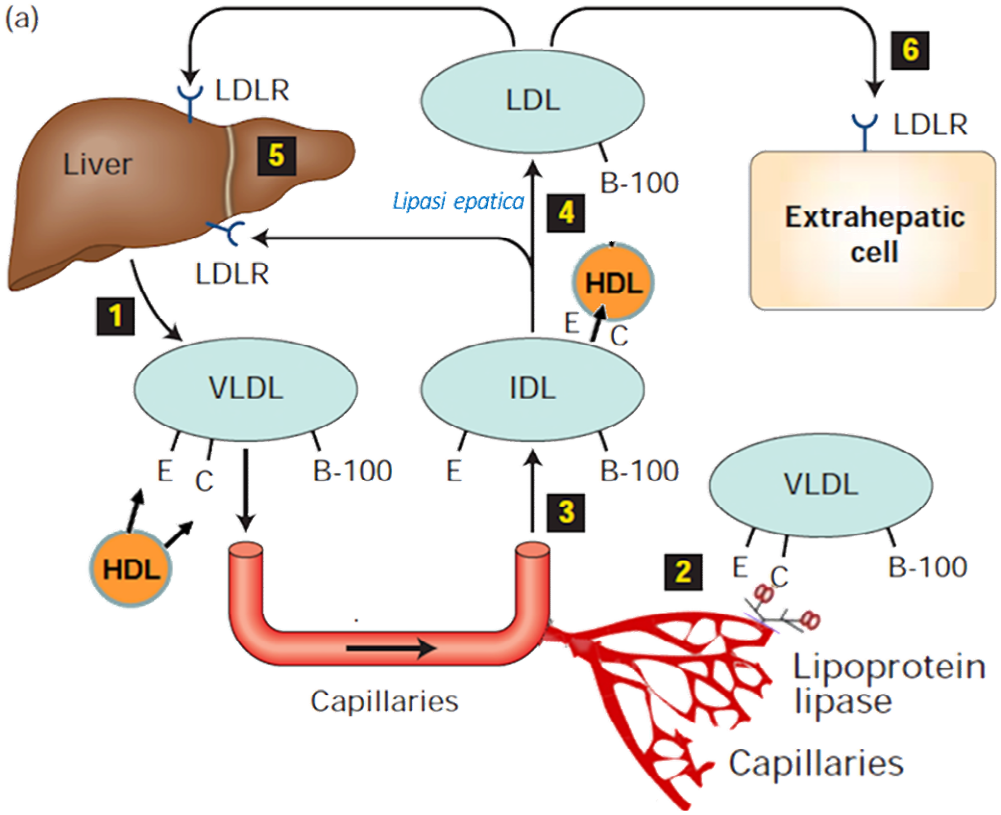
LIPOPROTEIN FUNCTIONS – VLDL, IDL & LDL

VLDL



LDL



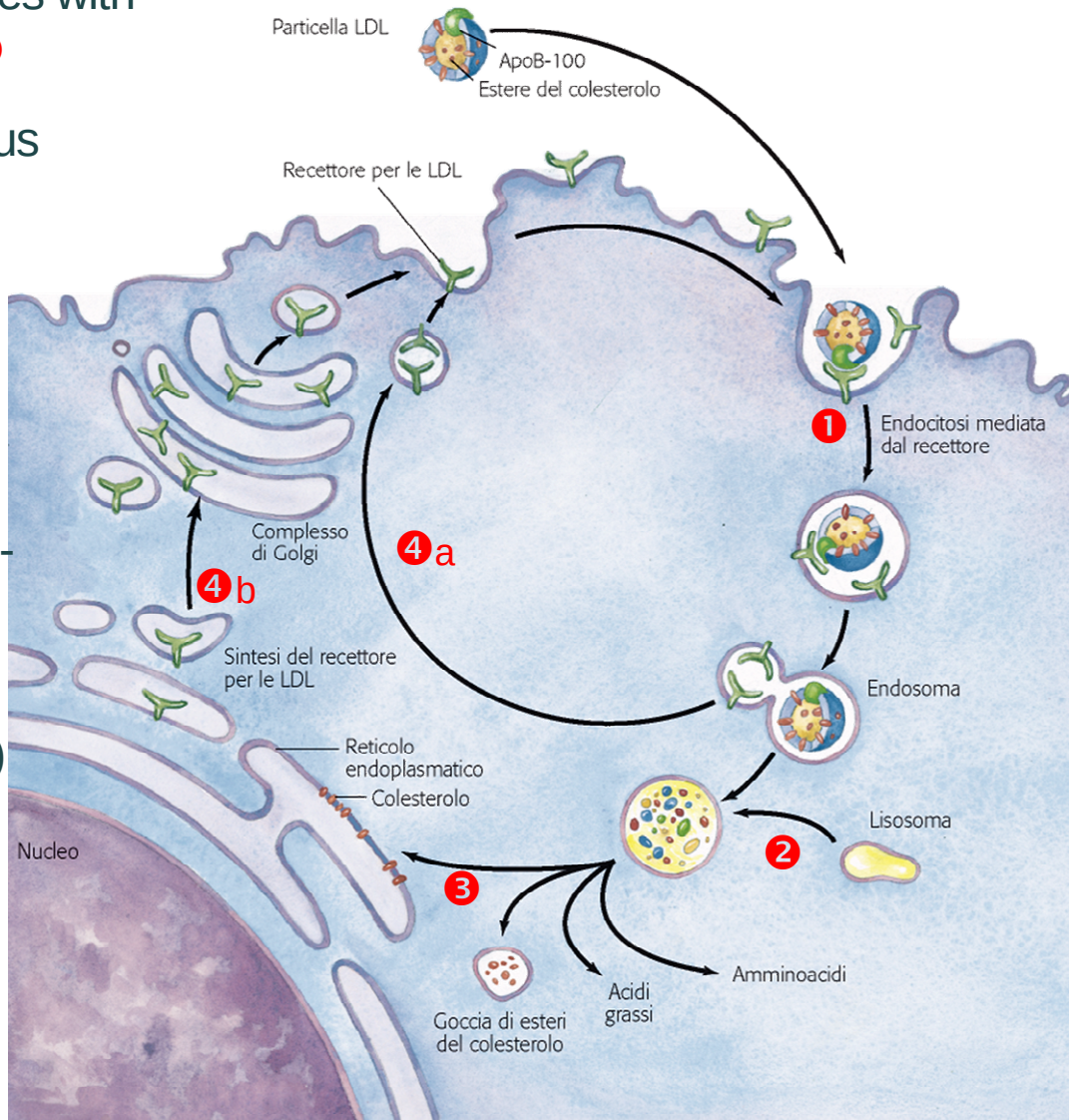


- **VLDL form in hepatocyte RE**
- They carry **ApoB100**, and are secreted directly into the bloodstream ❶. They acquire **ApoC** and **ApoE** from **HDL** and transfer **CLE** to **HDL**, using **CETP**
- They bind ***Lipoprotein lipase*** on capillary endothelia (via **Apo C**), which releases **AG** and **MAG** for translocation into cells ❷.
- Remnants (**IDL**) move to the liver, returning **ApoE/ApoC** to **HDL** ❸. Partly absorbed for recycling ❺, or more TAG are removed (❹ by ***Hepatic lipase***) and become **LDL**, highly enriched in **CL** which they transport to tissue LDL receptor (LDLR) ❻ for internalization

LIPOPROTEIN FUNCTIONS – LDL

LDL transport cholesterol to tissues

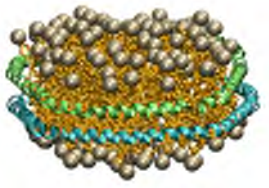
- They are taken up by **receptor-mediated endocytosis** mediated by **ApoB100** ❶
- They enter an **endosome** that then fuses with a **lysosome** and **LDL are degraded** ❷
- **CL and CLE released** ❸ e CL can be us as a membrane component or for the synthesis of steroid hormones
- The LDL receptor (**LDLR**) is in part recycled ❹a and in part degraded
- If degraded it must be re-expressed and sent to the membrane by the Golgi-dependent secretory pathway ❹b.
- Expression is regulated by SREBP via the Sterol Sensing Domain (SDS) of SCAP (Module 2_2 slides 7,9)
- Regulating LDLR recycling and expression regulates LDL entry



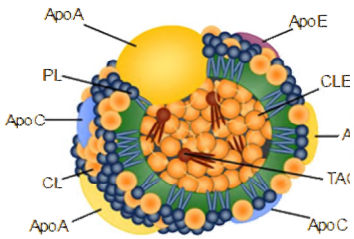
LIPOPROTEIN FUNCTIONS – HDL

HDLs are built from ApoA1 (liver & intestine)

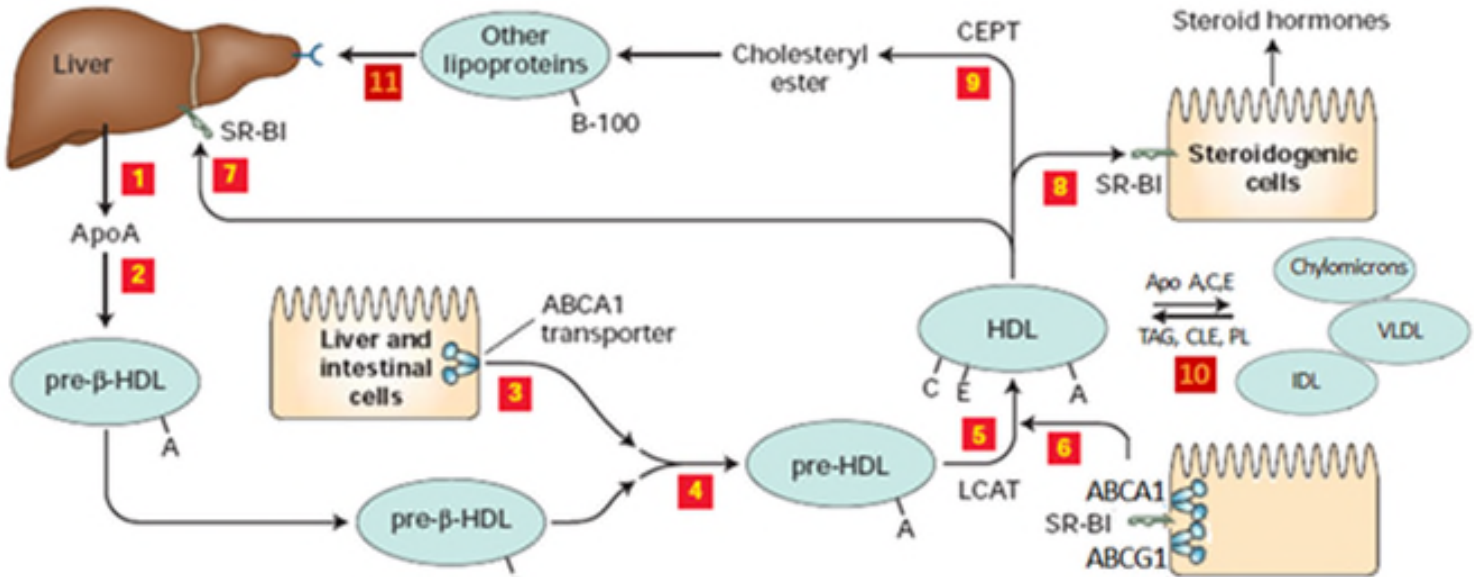
- **ApoA1**, secreted from hepatocytes ❶ (in **VLDL**), forms **pre-β-HDL** particles ❷ with little lipid.
- These load **PL** and **CL** from hepatocytes, enterocytes or adipocytes❸ (***ABCA1*** transporters).
- **pre-HDL** particles form that are enriched in **CL** ❹.
- **CL** esterifies to **CLE** (plasma enzyme ***Lechitin-CL acyltransferase*** (***LCAT***) in **mature HDL** ❺
- **HDL collect ApoE/C** from **remnants**, & **PL/CL** from tissues with ***ABCA1***/***ABCG1*** transp. ❻
- **HDL return CL** to **hepatocytes** ❼ or **steroidogenic cells** ❽via ***scavenger receptor SR-B1***
- **HDL exchange CL** (via **CETP)** ❾ and **ApoE/C** ❿ with other lipoproteins (**CM**, **VLDL**, **IDL**)
- These are an **alternative method** ⓫ to **return CL to hepatocytes** using receptors **LDLR** and **LPR** for remnants. **Excess CL** returned to liver is **excreted as bile**



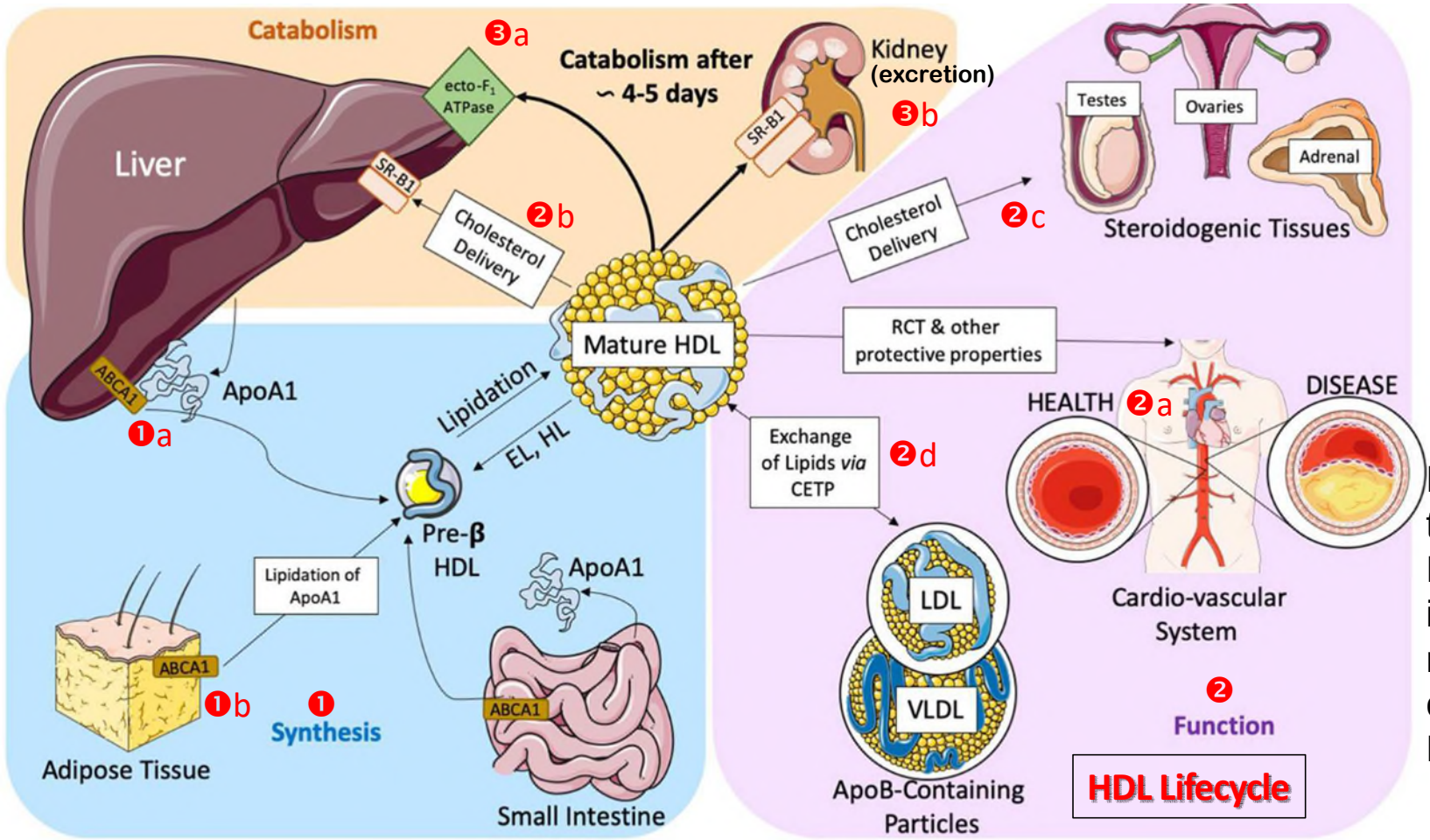
pre-β-HDL



HDL



THREE KEY STAGES OF THE HDL LIFECYCLE



ecto-F1 ATPase

"*moonlighting*" mitochondrial protein (F1 subunit of *ATP synthase*)

Produces ADP that stimulates $P2Y_{13}$ rcptr to initiate clathryn mediated endocytosis of HDL

① **Synthesis**: ApoA1 from liver/gut is loaded on-site via ***ABCA1*** (a) or at adipose tissue (b) to produce **pre-ß HDLs**. Mature **HDL** form by lipidation and return to **pre-ß HDL** by ***endothelial*** (***EL***) and ***hepatic lipases*** (***HL***) .

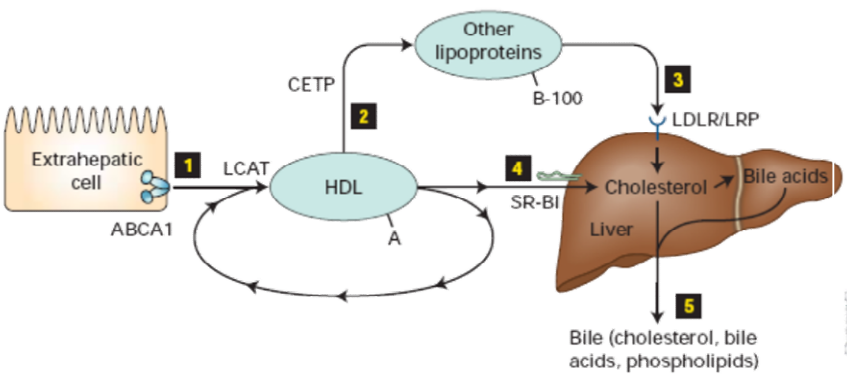
② **Function**: To efflux CL(CLE) from peripheral tissues (e.g. cardio-vascular system) (a) and transport it either to (b) the liver for disposal, (c) steroidogenic tissues or (d) exchange it with other lipoproteins.

③ **Catabolism**: After ~4/5 days, **HDL** is internalized into hepatocytes via ***ecto-F1 ATPase***, and both *ApoA1* and **CL** recycled/eliminated. Or it binds to scavenger receptor **SR-B1** in kidney and ApoA1 catabolized/excreted

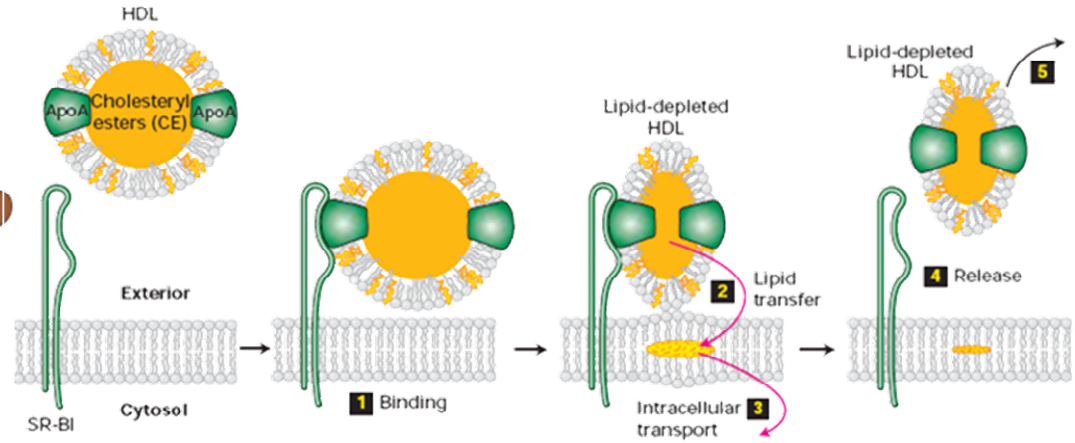
LIPOPROTEIN FUNCTIONS – M.O.A

HDL returns excess cholesterol from the tissues to the liver (Reverse Cholesterol Transport)

FUNCTION



MODE-OF-ACTION

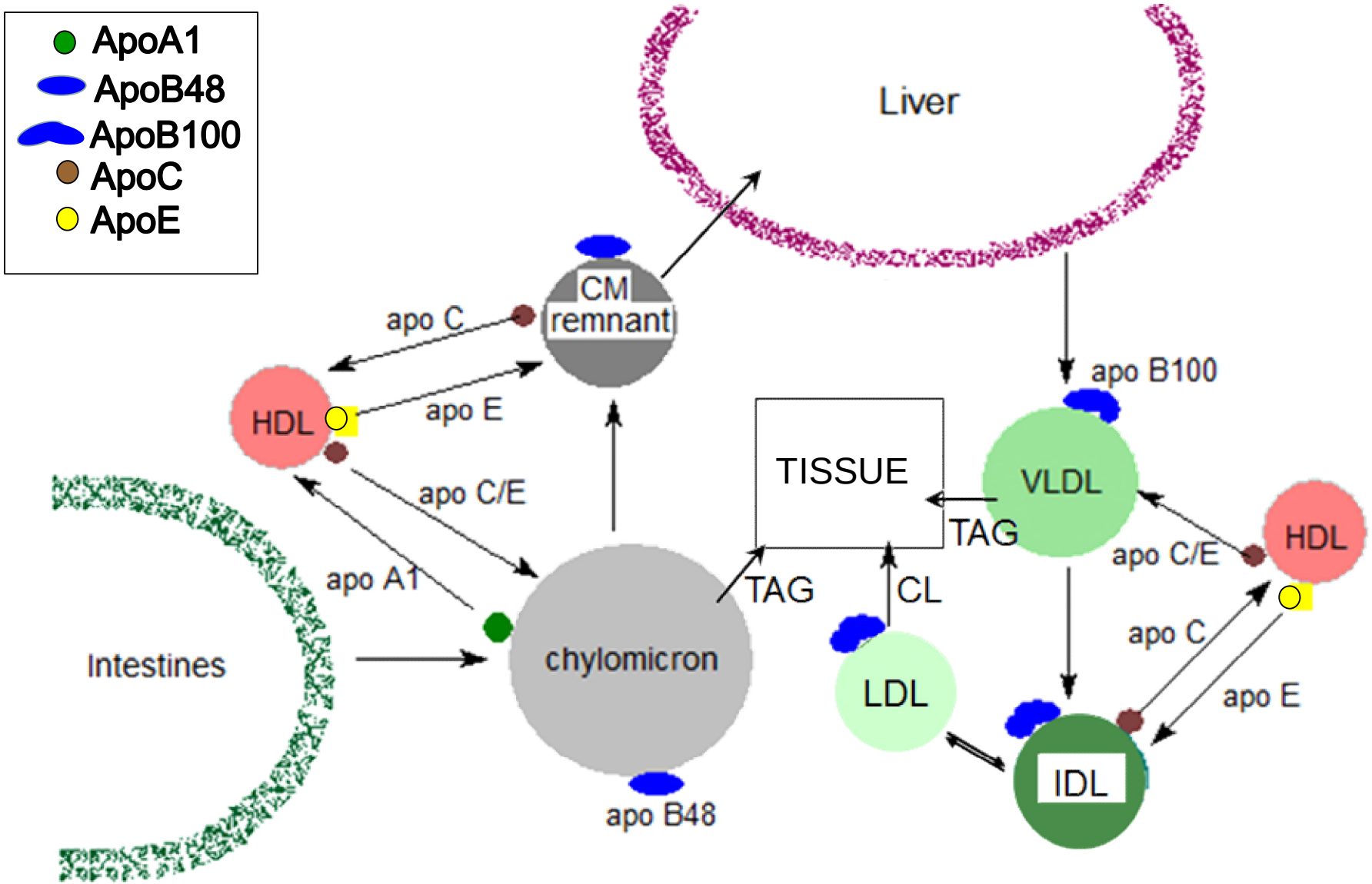


1. **Collect CL** from cells via ***ABCA1/ABCG1***
2. **Exchange CLE** with other lipoproteins (VLDL/CM) via **CETP**
3. **Return of CL** by **other lipoptoteins,** via LDLR e LRP
4. **Return of CL** by HDL and *Scavenger Receptor* **SR-B1**
5. **Reuse of CL** by liver or **Elimination in bile**

1. **HDL binds to the SR-B1,** which positions cholesterol-laden HDL close to membrane
2. **Transfer of CLE to the membrane**
3. **Transfer of CLE to cytosolic CLE Binding Protein** for intracellular transport.
4. **CLE-depleted HDL** detaches from SR-B1
5. **HDL return to the circulation** and resume their activity of taking up excess CL

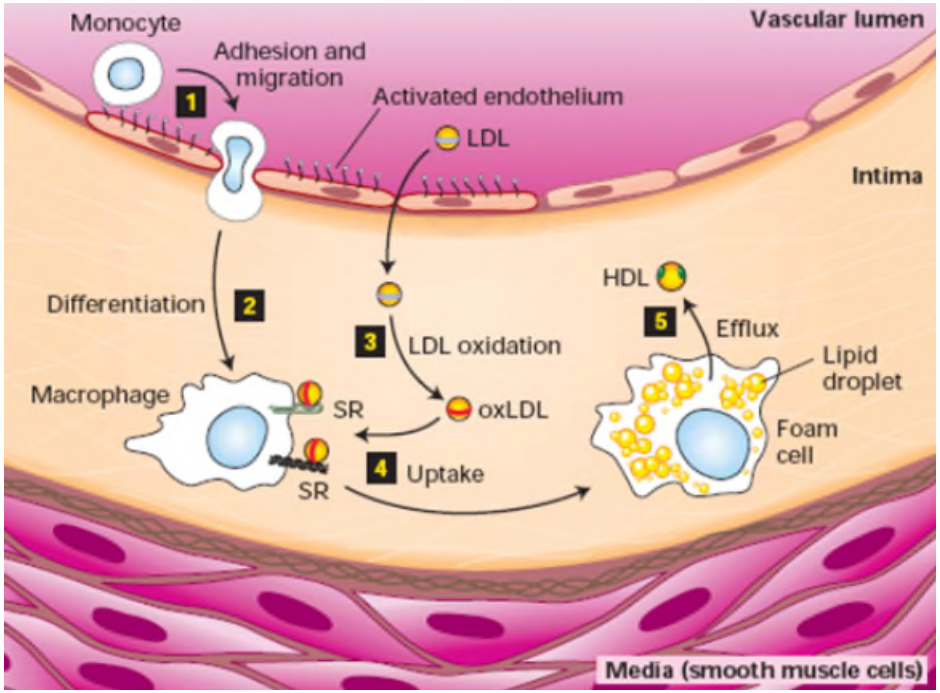
LIPOPROTEIN EXCHANGE

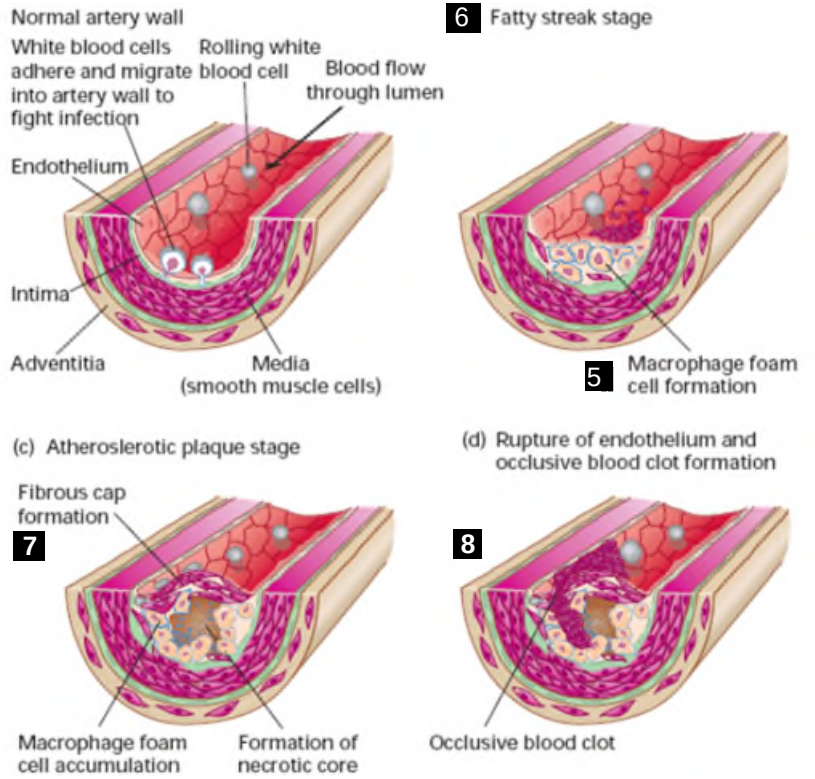
- **Lipoproteins exchange lipids and ApoProteins**



LIPOPROTEIN DISREGULATION

Excess LDL can cause atherosclerosis





1 Infection, inflammation or tissue damage can result in LDL (especially if excessive) entering the *intima*, the layer just below endothelial tissue in the arteries as well as immune cells (e.g. monocytes)

2 monocytes differentiate into macrophages **3** LDL contents become oxidized and oxLDL is recognized *scavenger receptors* **SR** on macrophages, leading to phagocytosis and degradation.

4 CLE accumulate in macrophages, forming droplets, and resulting in so-called ‘foam cells’.

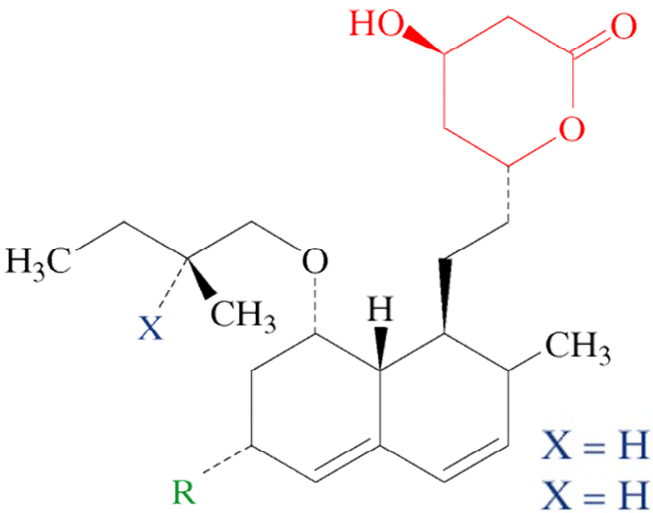
5 Macrophages can pass CLE to HDL via ABCA1, but if levels are unbalanced, foam cells accumulate.

6 This leads to the formation of ‘fatty streaks’, then leads to **7** necrosis and the formation of a fibrous cap

8 eventuallu an atherosclerotic plaque or atheroma

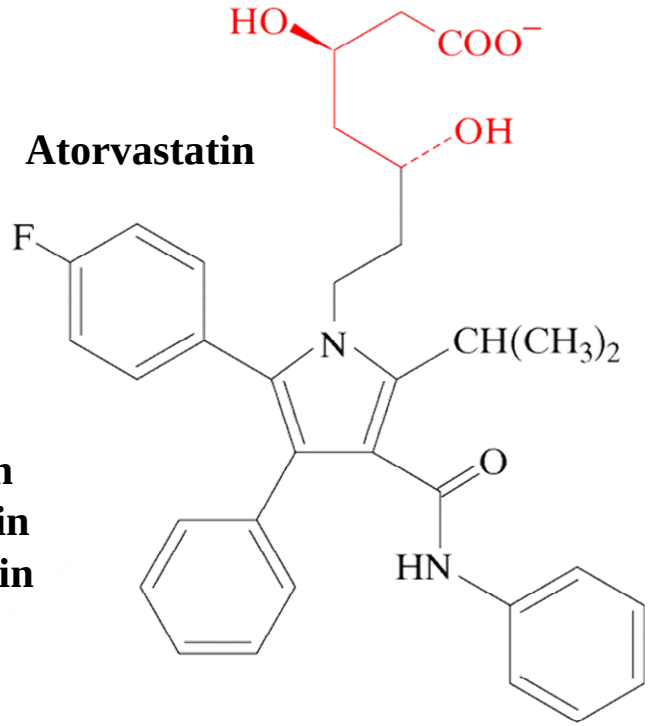
STATINS LOWER CHOLESTEROL BY INHIBITING SYNTHESIS

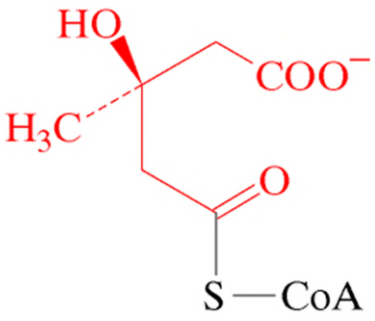
- **Statins – inibitors of *HMG-CoA reductase***



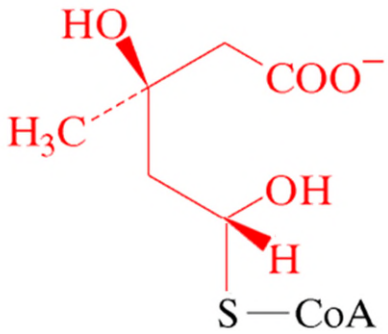
X = H R = CH_3 **Lovastatin**
X = H R = OH **Pravastatin**
X = CH_3 R = CH_3 **Simvastatin**

Atorvastatin

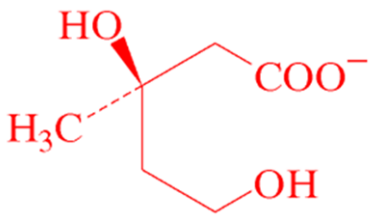




HMG-CoA
(substrate)



Mevaldyl-CoA
(transition state analog)



Mevalonate
(product)

- *Pleurotus ostreatus* contains lovastatin (< 3% dry weight)

- Lovastatin is normally derived from the fermentation broth of fungi belonging to the genus *Aspergillus,* preferably *Aspergillus terreus.*
- The related drug simvastatin is also produced