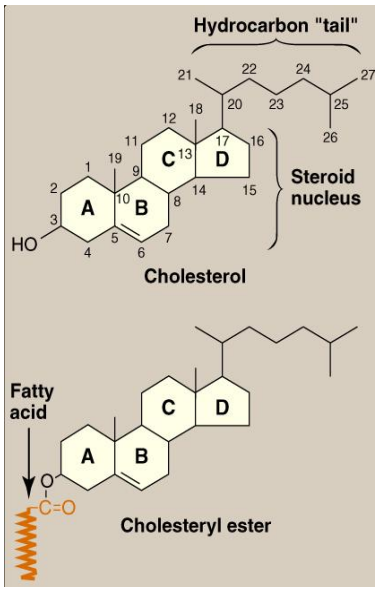
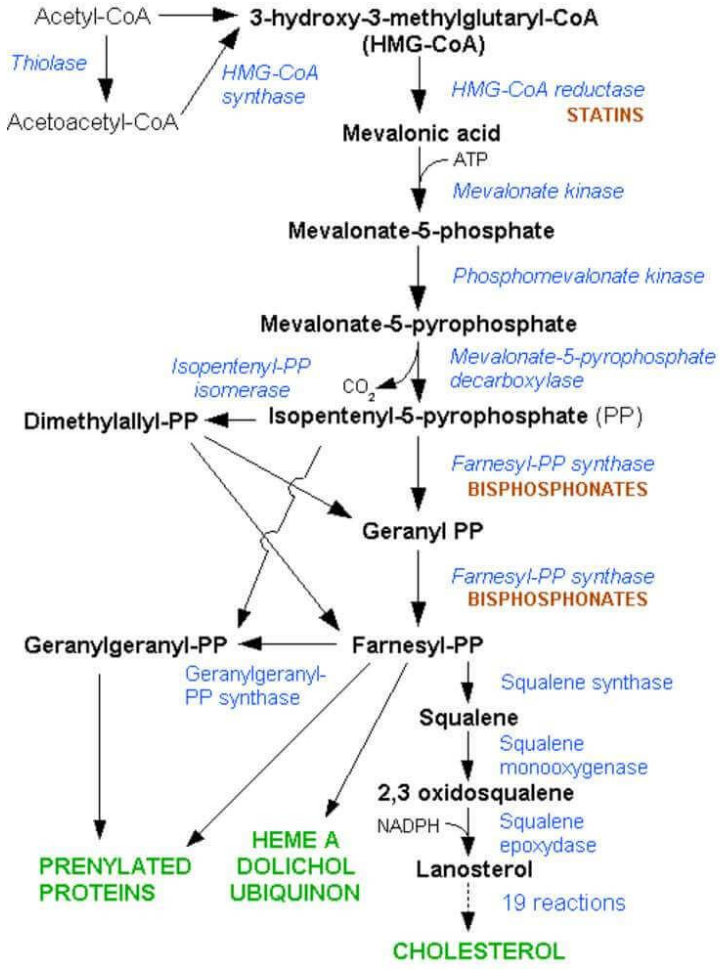
Unit IV – Problem 3 – Biochemistry: Cholesterol Metabolism and Lipoproteins

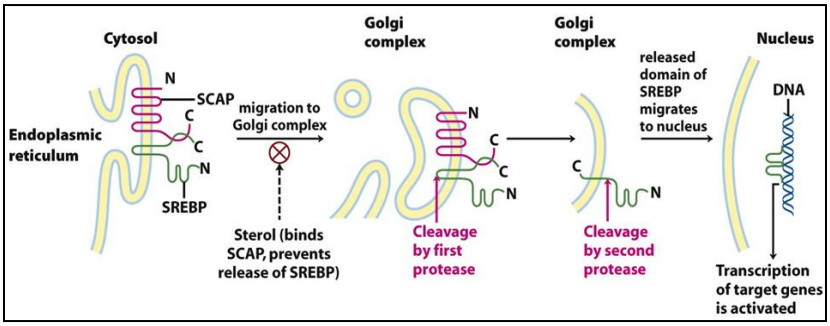
- **Cholesterol:**
  - **It is a sterol which is found in all eukaryotic cells and contains an oxygen (as a hydroxyl group –OH) on Carbon number "3".**
  - **Functions:**
    - ✓ Structural component of cell membrane modulating its fluidity.
    - ✓ Precursor of several hormones.
    - ✓ Converted to bile acid/salts in the liver and secreted when eating fatty meals (to aid in the digestion and absorption of dietary fat).



  - **Most of cholesterol is synthesized in our body and not obtained from diet. It is synthesized from acetyl CoA in 5 stages (this process takes place in the cytosol). The following are major sources of liver cholesterol:**
    - ✓ Dietary cholesterol which is transported to the liver by chylomicrons.
    - ✓ Cholesterol synthesized in extrahepatic tissues and transported to the liver through HDL.
    - ✓ De novo synthesis of cholesterol in the liver.
  - **Synthesis of cholesterol:**
    - ✓ Site: cytosol of liver and intestine.
    - ✓ Over accumulation of cholesterol will result in deposition of cholesterol-rich lipoproteins in coronary arteries leading to → atherosclerosis.

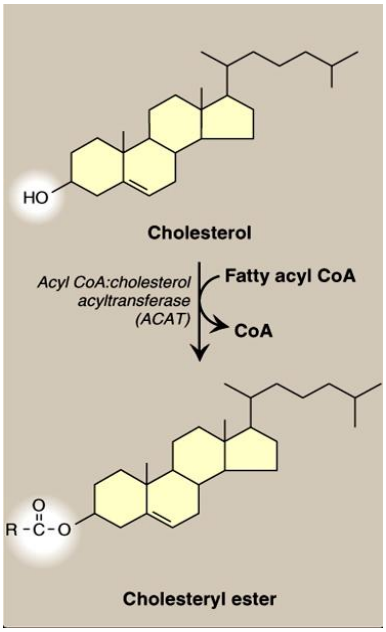


- ✓ Regulation of cholesterol synthesis:
  - ❖ *HMG CoA reductase:*
    - ➢ Short-term regulation: HMG CoA reductase is inhibited by phosphrylation (adding phosphate) which is catalyzed by AMP-kinase.
    - ➢ Long-term regulation: feedback inhibition of HMG CoA reductase by cholesterol itself.
  - ❖ *Hormonal regulation:*
    - ➢ Insulin: it activates HMG CoA reductase thus resulting in ↑ synthesis of cholesterol.
    - ➢ Glucagon: it inhibits HMG CoA reductase thus resulting in ↓ cholesterol synthesis.
  - ❖ *Transcriptional regulation:*
    - ➢ The expression of the gene for HMG CoA reductase is controlled by the transcription factor SREBP-2 (Sterol Regulatory Element Binding Protein – 2).



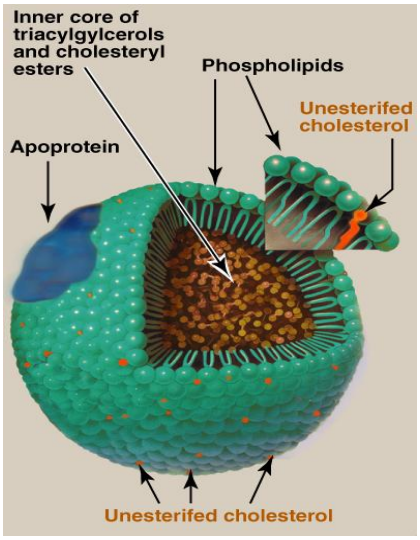
  - ❖ *Drugs:*
    - ➢ Statins: they are lipid-lowering agents which decrease cholesterol levels by competitive inhibition of HMG CoA reductase. Examples include: atorvastatin (Lipitor) and rosuvastatin (crestor).

- **Intracellular cholestryl ester:**
  - ✓ Cholesterol which is present in the plasma will be esterified by a fatty acid and converted to → cholesteryl ester (which is more hydrophobic than free cholesterol).
  - ✓ Notice that free cholesterol and cholesteryl ester are both hydrophobic (don't like water) → therefore, they are transported in such environment by being carried in lipoproteins.

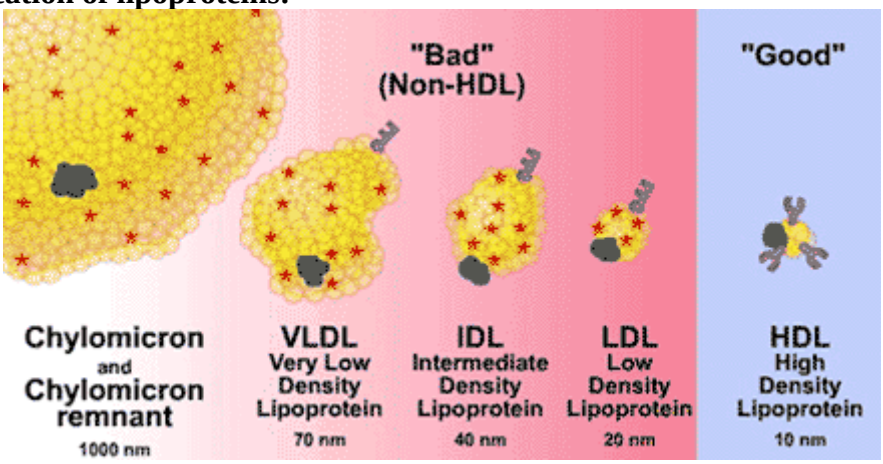


- **Degradation of cholesterol:**
  - ✓ Conversion to bile acids/salts → which are lost with feces.
  - ✓ Secretion of cholesterol itself with the bile → which will be transported to intestine for elimination.

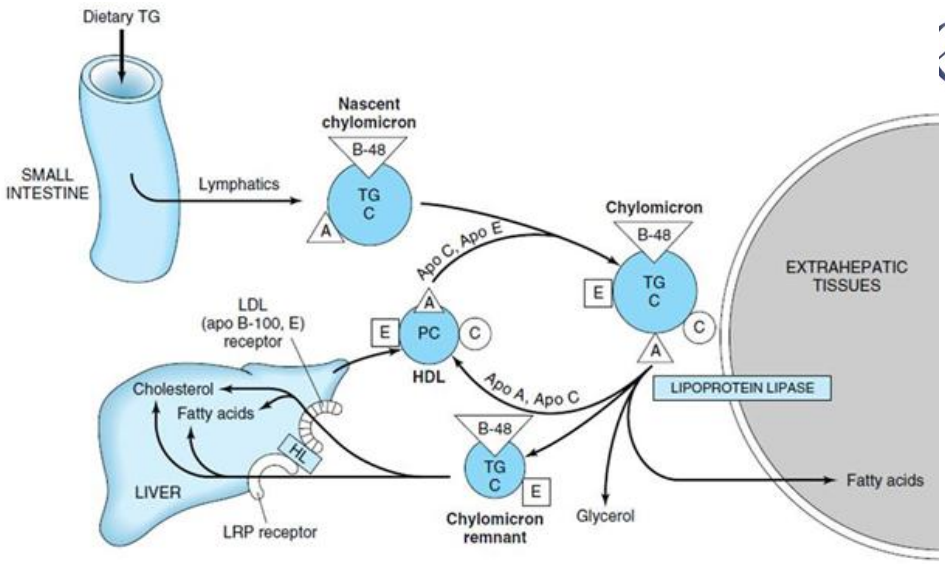
- **Lipoproteins**:
  - **They are cluster of proteins and lipids which transport lipids in the blood.**
  - **All lipoproteins are composed of:**
    - ✓ Core of lipids: apolar lipids (triacyglycerols and cholesteryl esters).
    - ✓ Surface coat: polar lipids (phospholipids and free cholesterol).
    - ✓ Apolipoproteins:
      - ❖ *They are lipid-binding proteins which function as:*
        - ➢ Structural components of lipoprotein particles.
        - ➢ Cofactors for enzymes.
        - ➢ Ligands for cell surface receptors.
      - ❖ *Apolipoproteins are divided into 5 classes (Apo-A, Apo-B, Apo-C, Apo-D and Apo-E) with each class being further subdivided into subclasses.*



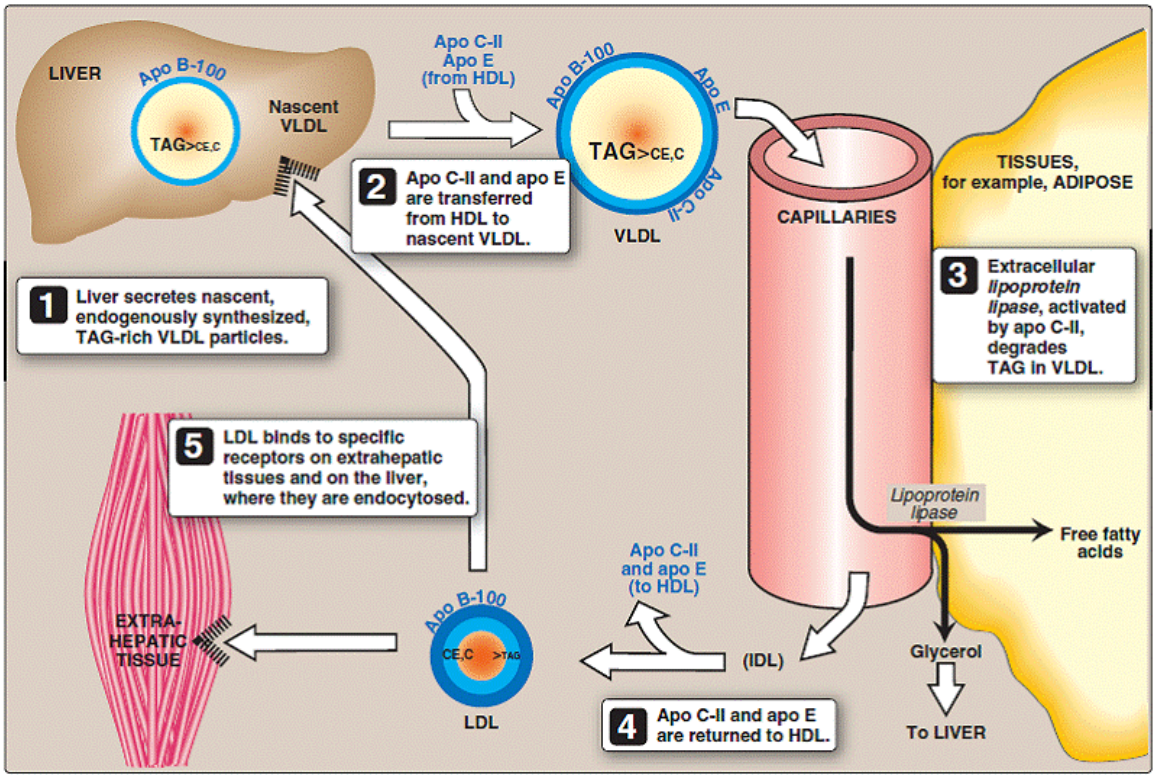
  - **Classification of lipoproteins:**



  - **Metabolism of chylomicrons:**
    - ✓ Function: they transport dietary lipids to the liver and adipose tissues.
    - ✓ They are produced in enterocytes (in rough endoplasmic reticulum).
    - ✓ Assembly of chylomicrons:
      - ❖ Loading of Apo-B48 with lipid (by microsomal transfer protein).
      - ❖ Transition from endoplasmic reticulum to Golgi and Packaging into secretory vesicles.
      - ❖ Vesicles will fuse with the membrane and release the incomplete chylomicrons in lymphatic vessels first and then into the blood stream.
      - ❖ ApoCII and ApoE will be added to the incomplete chylomicron.
    - ✓ Formation of chylomicron remnants:
      - ❖ Loss of TAG by lipoprotein lipase.
      - ❖ ApoCII return to HDL.
      - ❖ Remnant is taken up by the liver (through ApoE receptor) for degradation.



- **Metabolism of VLDL:**
  - ✓ Function: transports endogenous products to adipose tissues and muscles.
  - ✓ VLDL is assembeled in the liver from: triglycerides, cholesterol, cholesteryl ester and apolipoproteins (Apo-B100, Apo-CI and ApoE).
  - ✓ Formation of VLDL remnant (LDL):
    - ❖ TAG is degraded by lipoprotein lipase.
    - ❖ VLDL decreases in size (IDL).
    - ❖ ApoC and ApoE return back to HDL.
    - ❖ IDL is converted to LDL.



- **Metabolism of HDL:**
  - ✓ It is the smallest and most dense lipoprotein.
  - ✓ Structure:
    - ❖ Discoid in shape containing phophatidylcholine (lecithin).
    - ❖ It contains several lipoproteins (ApoA, ApoC and ApoE).
    - ❖ It changes into sphere when cholesterol is added.
  - ✓ HDL is synthesized in the liver → it picks up cholesterol from cells and esterify them by PCAT/LCAT → accumulation of cholesteryl esters will

convert HDL3 (poor) to HDL2 (rich) → then it will lose Apo-AI and bind to liver cells → **in the liver, cholesterol is:**

- ❖ *Changed to bile acids/salts.*
- ❖ *Disposed via bile.*
- ❖ *Transported to steroidogenic cells for hormone synthesis.*

- **Lipoprotein (a):**
  - ✓ It is another kind of atherogenic lipoprotein which consists of LDL + apo (a)
  - ✓ Notice that high level of apo (a) is associated with premature Coronary Artery Disease (CAD) and stoke.
  - ✓ Lipoprotein (a) is highly resistant to diet and drug therapy.

TABLE 356-3 Fredrickson Classification of Hyperlipoproteinemias

Phenotype	I	IIa	IIb	III	IV	V
Lipoprotein, elevated	Chylomicrons	LDL	LDL and VLDL	Chylomicron and VLDL remnants	VLDL	Chylomicrons and VLDL
Triglycerides	↑↑↑	N	↑	↑↑	↑↑	↑↑↑
Cholesterol (total)	↑	↑↑↑	↑↑	↑↑	N/↑	↑↑
LDL-cholesterol	↓	↑↑↑	↑↑	↓	↓	↓
HDL-cholesterol	↓↓↓	N/↓	↓	N	↓↓	↓↓↓
Plasma appearance	Lactescent	Clear	Clear	Turbid	Turbid	Lactescent
Xanthomas	Eruptive	Tendon, tuberous	None	Palmar, tuberoeruptive	None	Eruptive
Pancreatitis	+++	0	0	0	0	+++
Coronary atherosclerosis	0	+++	+++	+++	+/–	+/–
Peripheral atherosclerosis	0	+	+	++	+/–	+/–
Molecular defects	LPL and ApoC-II	LDL receptor, ApoB-100, PCSK9, LDLRAP, ABCG5 and ABCG8		ApoE	ApoA-V	ApoA-V and GPIHBP1
Genetic nomenclature	FCS	FH, FDB, ADH, ARH, sitosterolemia	FCHL	FDBL	FHTG	FHTG