HBC 302: METABOLISM II

LECTURE 1:Lipid Metabolism

Introduction, digestion, absorption and mobilization

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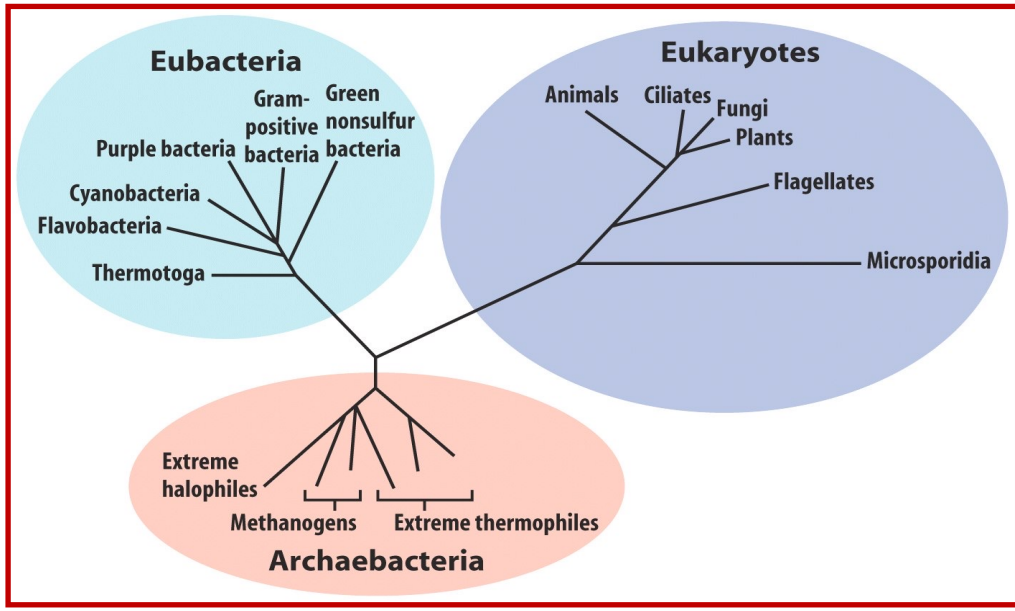
Course Outline

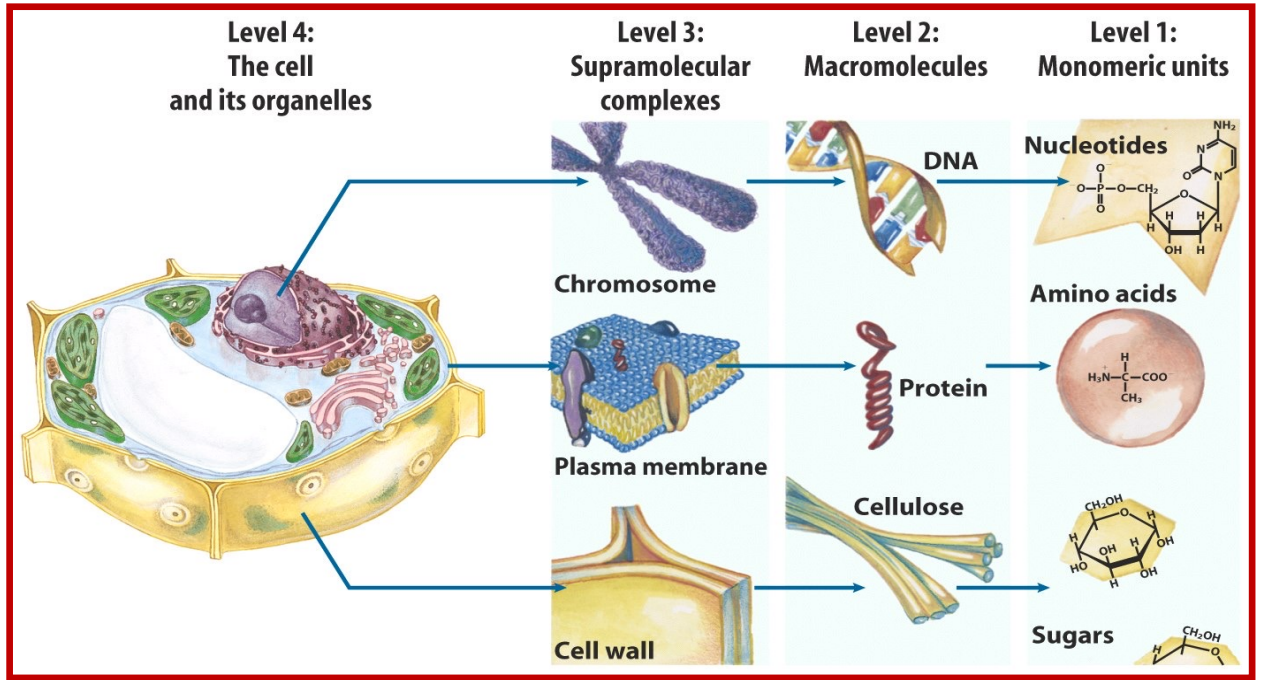
WEEK	DATE	TOPIC
1	03-10-2022 to 07-10-2022	Lipid Metabolism: Introduction, links to cabohydrate metabolism, digestion, absorption and mobilization
2	10-10- 2022 to 14-10-2022	Fatty axid oxidation, oxidation of saturated and unsaturated fatty acids, odd chain fatty acids, propionate metabolism.
3	17-10-2022 to 21 -10 -2022	Lipid biosynthesis: Fatty acid biosynthsis, sythesis of triacylglycerides and phospholipids.
4	24-10-2022 to 28-10-2022	Ketone bodies: Synthesis and breakdown, Glyoxylate pathway
5	31-10-2022 to 04-11-2022	Cholesterol biosynthesis, diseases associated with cholesterol metabolism
6	07 -11-2022 to 11 -11-2022	Amino acids and protein metabolism: Introduction, protein turnover, essential and non-essential amino acids, protein digestion and absorption
7	14-11-2022 to 18 -11-2022	Reactions of amino acids: transaminations, deaminations, carboxylations. CAT 1
8	21-11-2022 to 25 -11- 2022	Catabolism of amino acids: Glucogenic and ketogenic amino acids, fate of the carbon skeleton, fate of ammonia, urea cycle
9	28-11-2022 to 02-12-2022	Catabolism of individual amino acids Synthesis of individual amino acids
10	05-12-2022 to 09-12-2022	Formation of nitrogeneous products: Porphyrin metabolism, diseases associated with porphyrin metabolism, diseases associated with amino acid/protein metabolism
11	12 -12-2022 to 16 -12-2022	Purine and pyrimidine metabolism: Introduction, de novo and salvage pathways for synthesis of purines and pyrimidines
		CHRISTMAS BREAK
12	09-01-2023 to 13-01-2023	Breakdown of purine and pyrimidine containing nucleotides, synthesis of deoxyribose containing nucleotides
13	16-01-2023 to 20-01-2023	Nucleic acids replication, transription and translation CAT 2
14 & 15	23-01-2023 to 03-02-2023	UNIVERSITY EXAMINATIONS

What is Biochemistry?

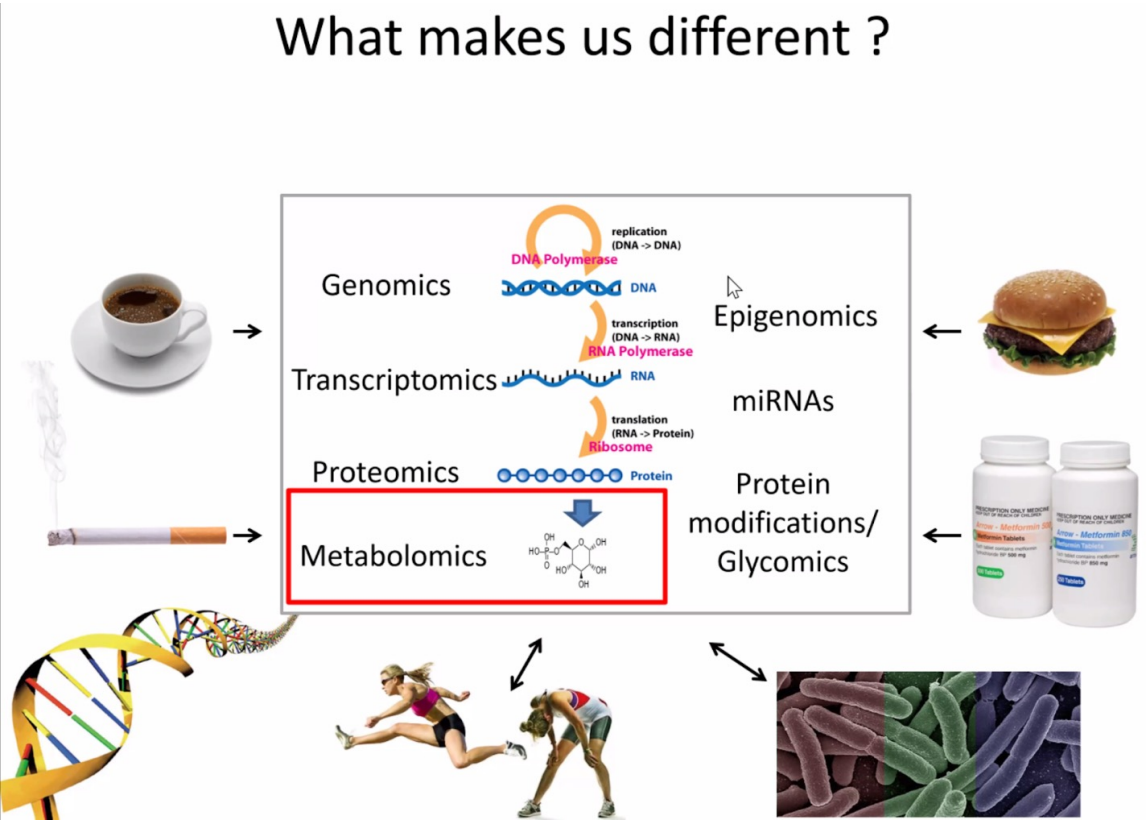
What is BIOCHEMISTRY

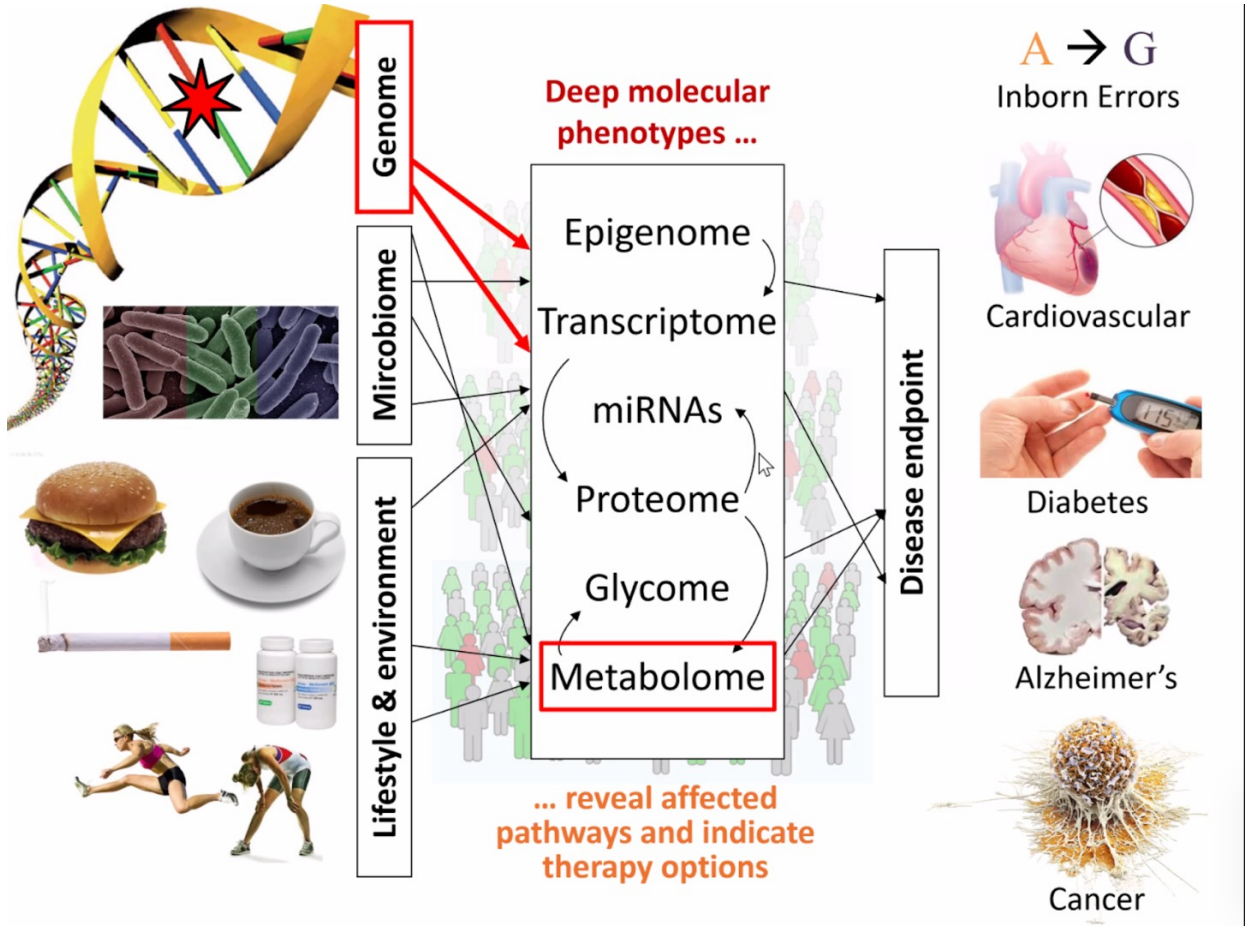
- Deals with the chemical processes and compounds of living organisms, from viruses, (archaea, bacteria, fungi, plants, to invertebrates and vertebrates
- Applies the tools and concepts of chemistry to living systems
- Analyzes the structure and physical properties and the function of biological molecules (proteins, carbohydrates, lipids, and specialized chemical compounds that make up living cells)
- Also studies the interaction between molecules in living organisms
- Analyzes the mechanisms and products of all reactions involved



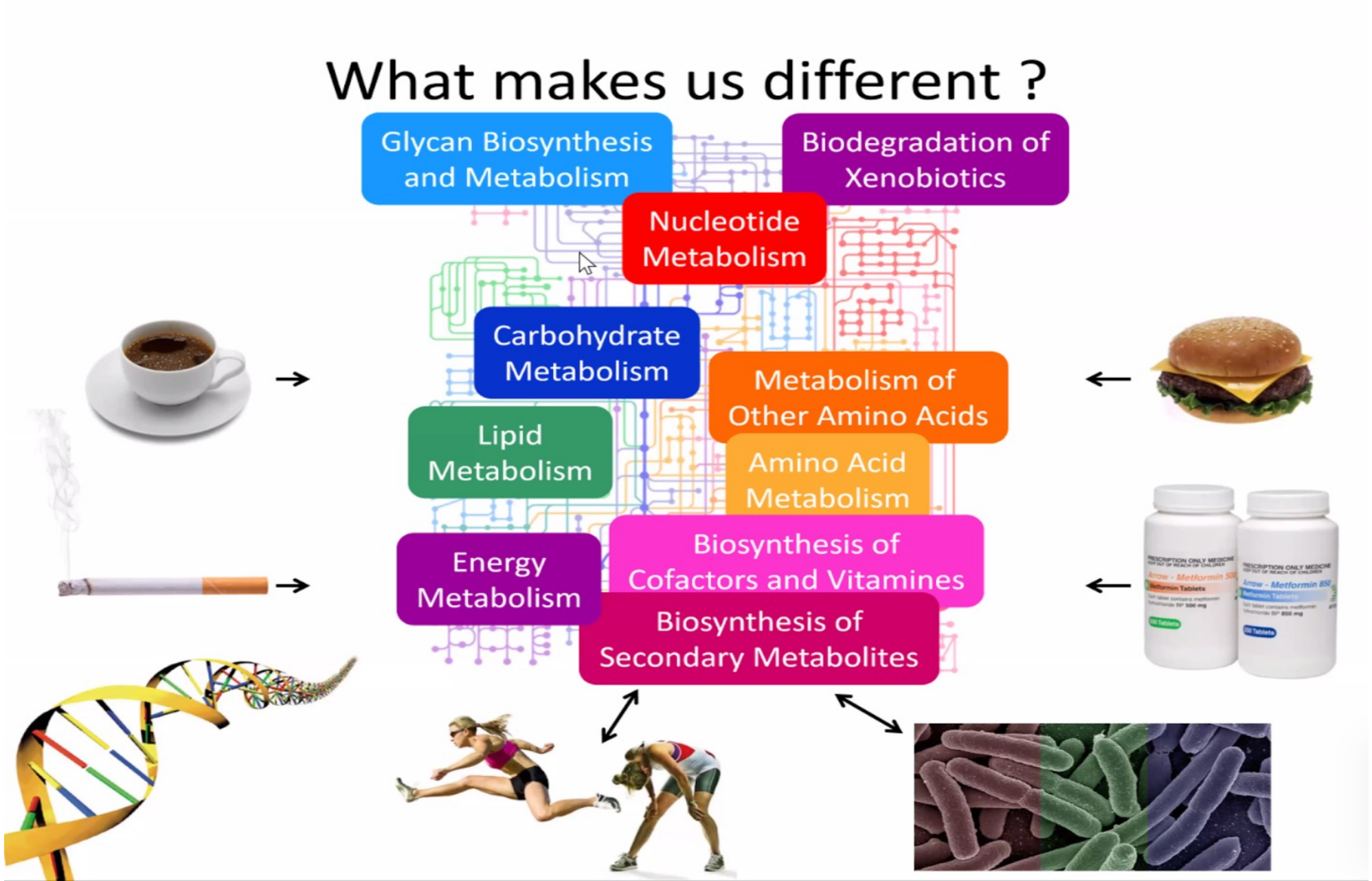


Why should you understand metabolism?

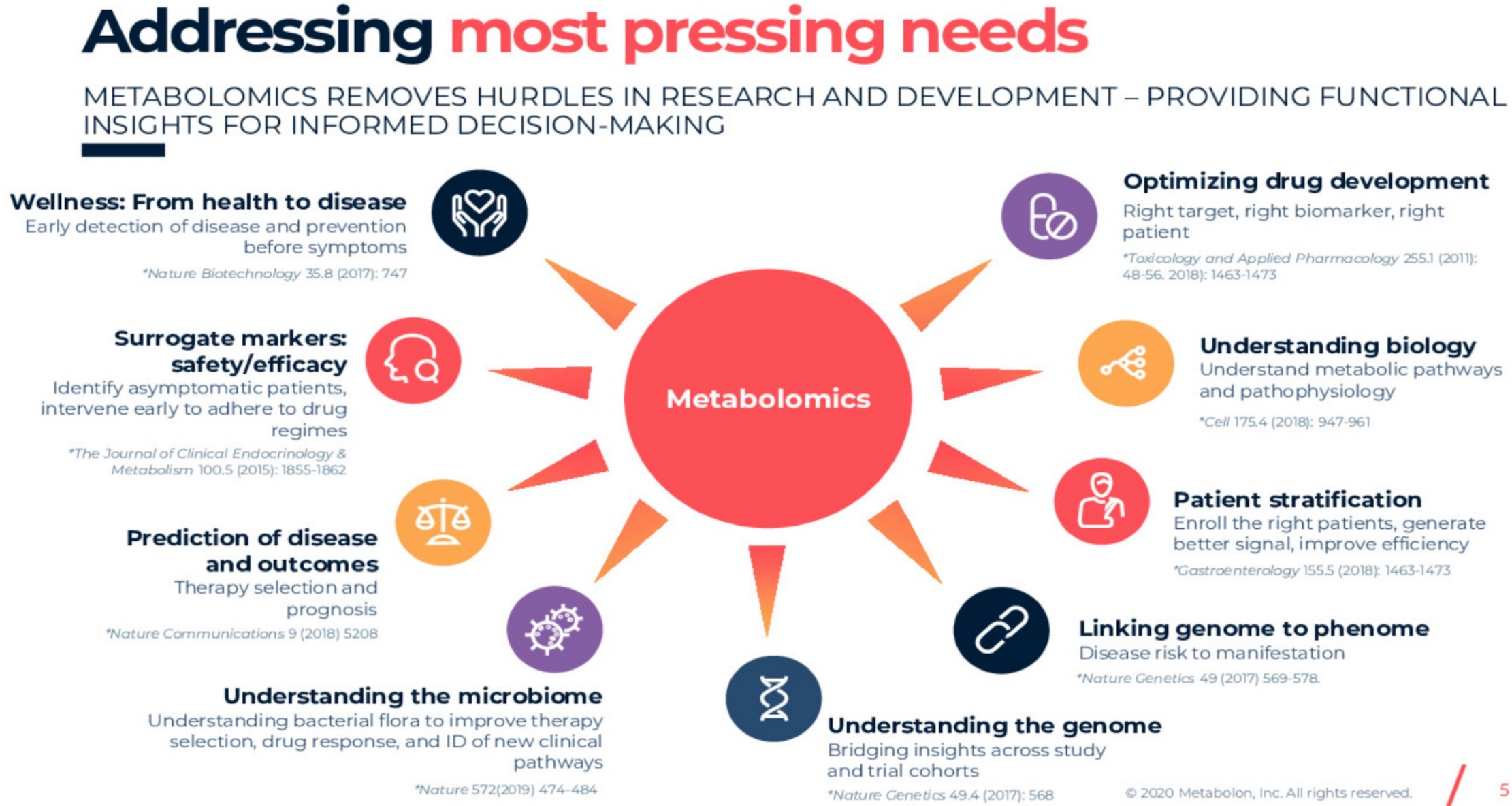




Why is it important?

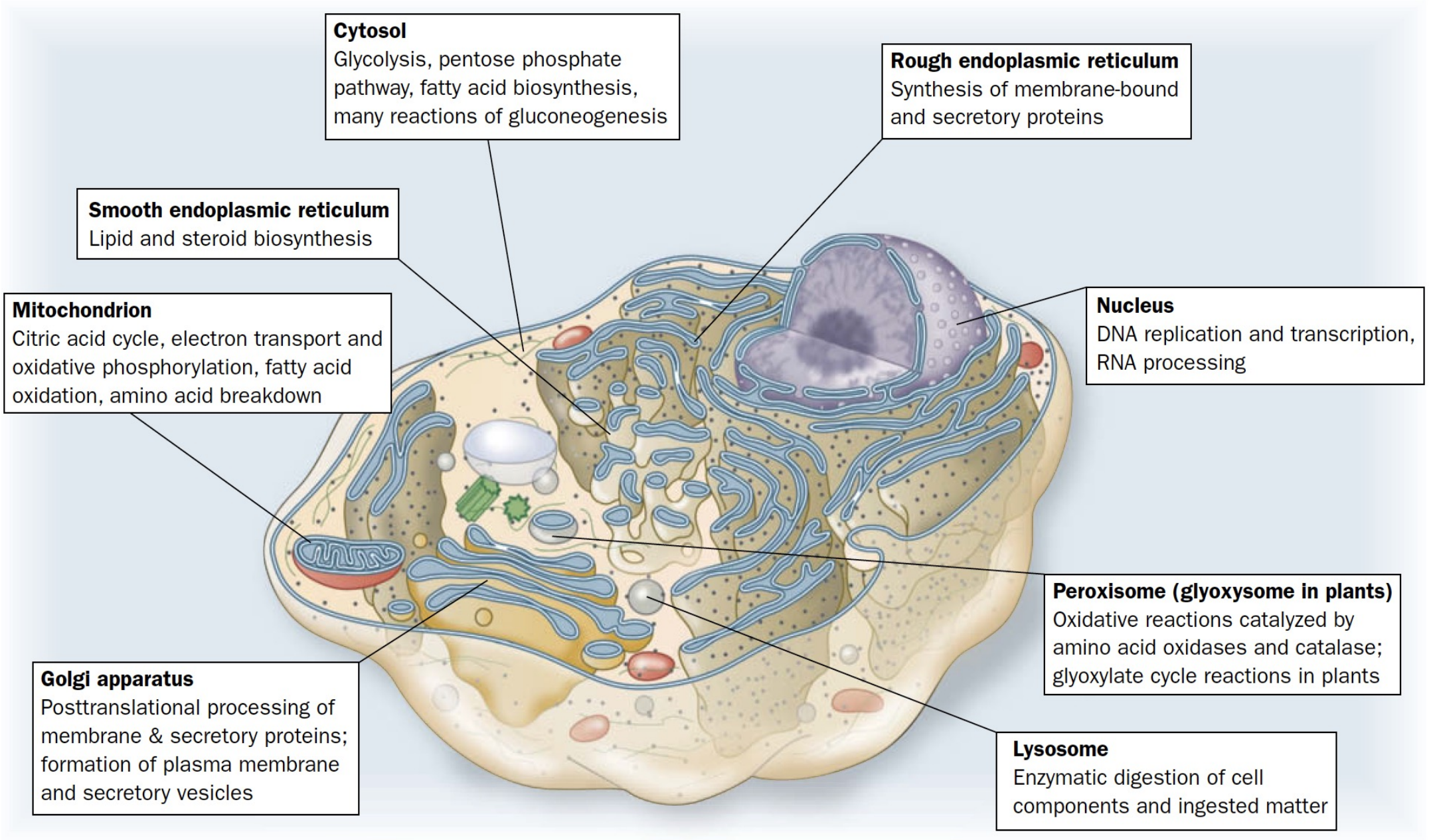


Why is it important?



Lipid Metabolism

Metabolic Pathways Occur in Specific Cellular Locations



LIPIDS – overview

- Lipids are a diverse group of compounds that are related by their insolubility in water.

- Membranes contain lipids, particularly phosphoglycerides, sphingolipids, and cholesterol.

- Triacylglycerols, which provide the body with its major source of energy,
  - Obtained from the diet or synthesized mainly in the liver.

- Lipids are transported in the blood as lipoproteins
  i. Chylomicrons,
  ii. very low-density lipoprotein (VLDL)
  iii. intermediate-density lipoprotein (IDL)
  iv. low-density lipoprotein (LDL)
  v. highdensity lipoprotein (HDL)

- Storage of of lipids ➔ Adipose tissue
  - In adipose cells, the fatty acids are converted to triacylglycerols and stored.

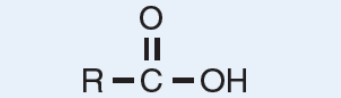
- Lipid mobilization
  - The triacylglycerols of chylomicrons and VLDL are hydrolyzed in the blood by lipoprotein lipase to fatty acids and glycerol.
  - During fasting, Fas (from adipose tissue) are oxidized to produce energy.
  - In the liver, fatty acids are converted to ketone bodies ➔ oxidized by muscle and kidney.

Structure of Lipids

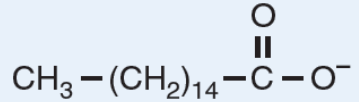
A. Fatty acids exist freely or esterified to glycerol

- In humans, fatty acids usually have an even number of carbon atoms, are 16 to 20 carbon atoms in length, and may be saturated or unsaturated (contain double bonds).
- Described by the number of carbons and the positions of the double bonds (e.g., arachidonic acid, which has 20 carbons and 4 double bonds, is 20:4, $\Delta^{5,8,11,14}$).
- All naturally occurring fatty acids have double bonds in the cis configuration.
- Polyunsaturated fatty acids are often classified according to the position of the first double bond from the ω-end (the carbon farthest from the carboxyl group; e.g., ω-3 or ω-6).

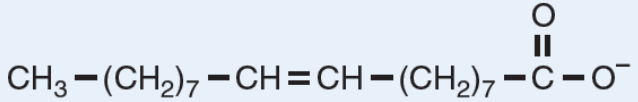
Fatty acids



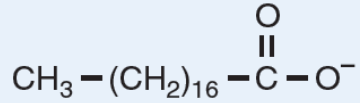
General structure



Palmitate (16:0)



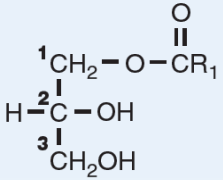
Oleate (18:1, Δ^9)



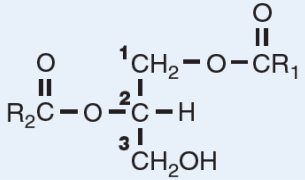
Stearate (18:0)

B. Monoacylglycerols, diacylglycerols and triacylglycerols contain one, two, and three fatty acids esterified to glycerol, respectively.

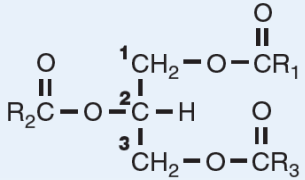
Monoacylglycerol (monoglyceride)



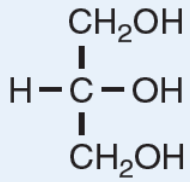
Diacylglycerol (diglyceride)



Triacylglycerol (triglyceride)

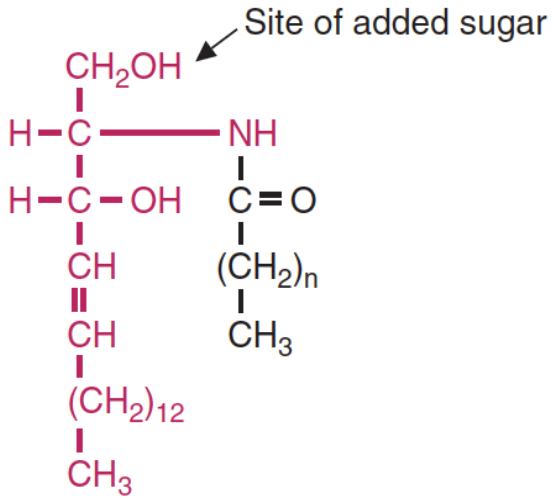


Glycerol



Structure of Lipids

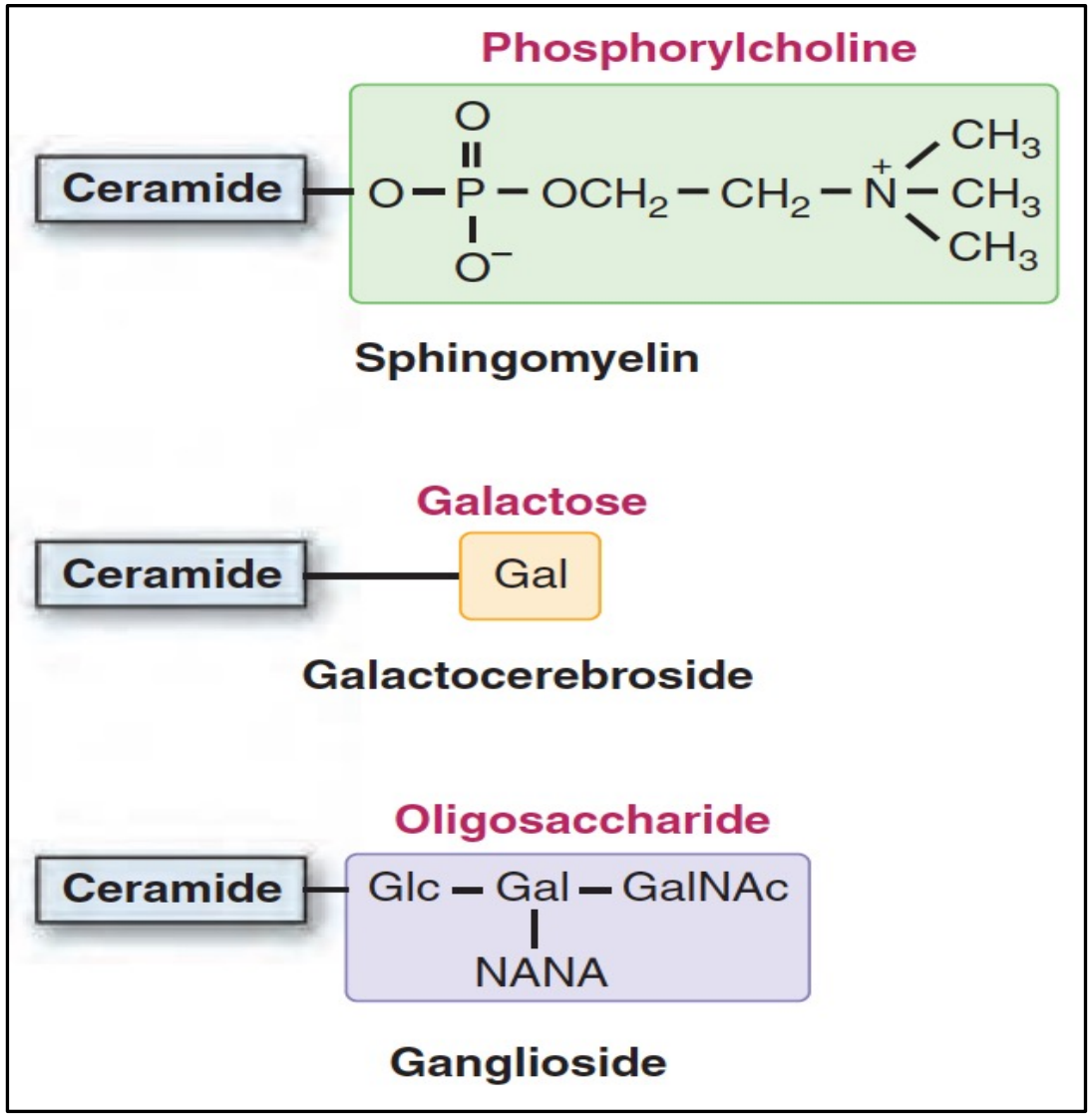
C. Phosphoglycerides contain fatty acids esterified to positions 1 and 2 of the glycerol moiety and a phosphoryl group at position 3 (e.g., phosphocholine).



Ceramide

D. Sphingolipids contain ceramide with a variety of groups attached

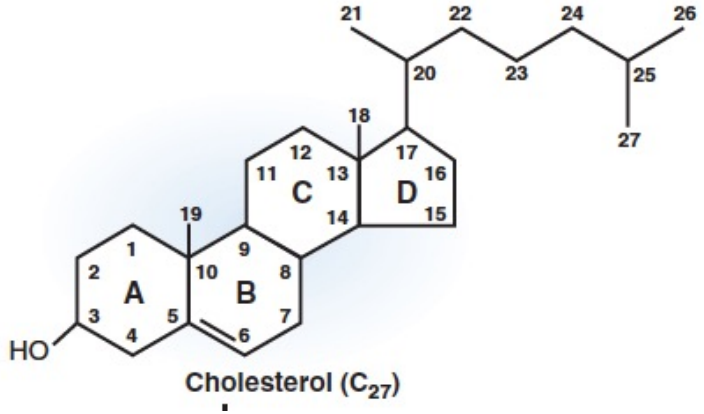
1. Sphingomyelin contains phosphocholine.
2. Cerebrosides contain a sugar residue.
3. Gangliosides contain a number of sugar residues, one of which is sialic acid.



Structure of Lipids

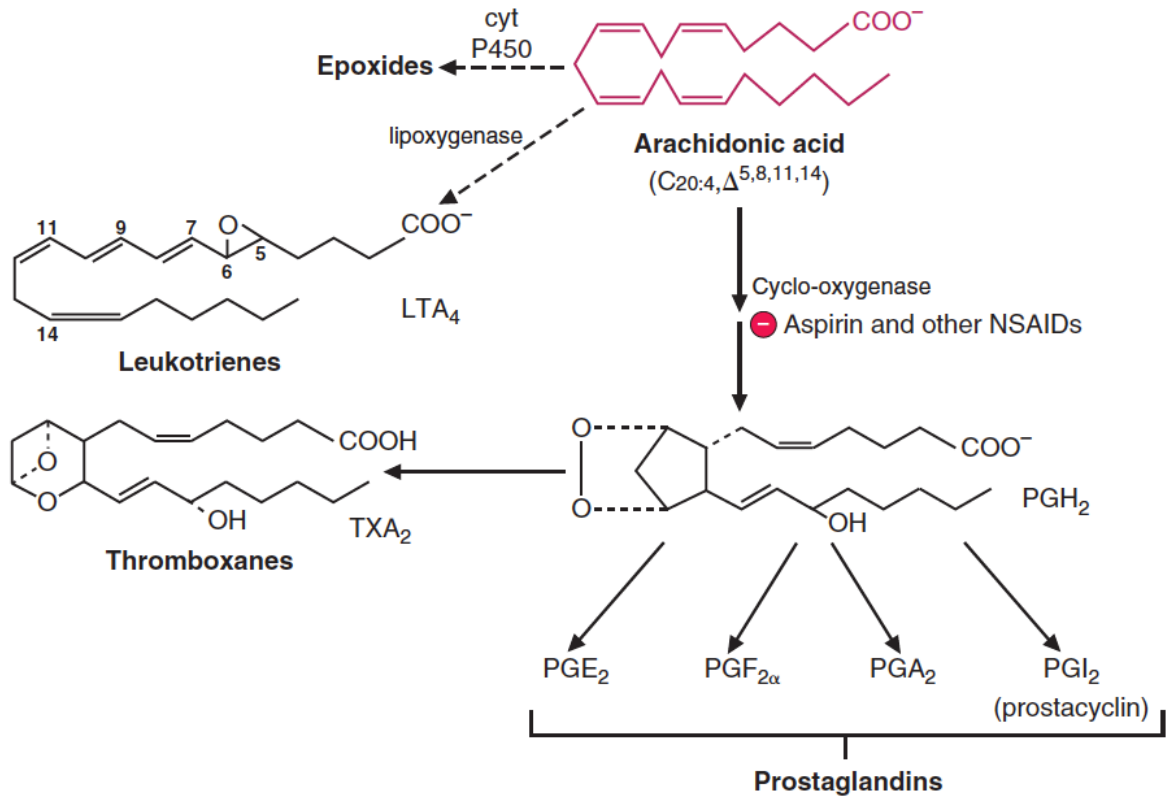
E. Cholesterol contains four rings and an aliphatic side chain

Bile salts and steroid hormones are derived from cholesterol



Cholesterol (C_{27})

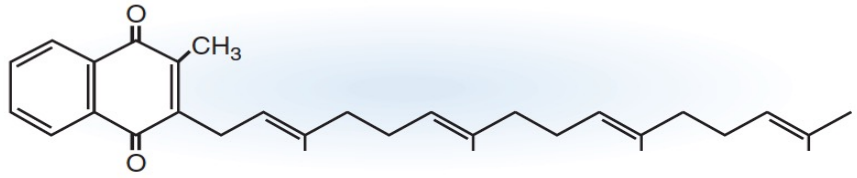
F. Prostaglandins and leukotrienes are derived from polyunsaturated fatty acids such as arachidonic acid.



Structure of Lipids

G. The fat-soluble vitamins include **vitamins A, D, E & K**

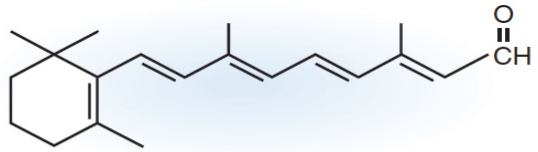
A. Vitamin K



Function

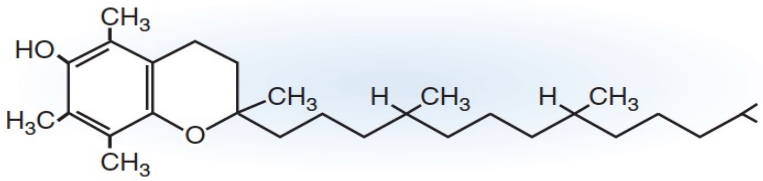
Blood clotting

B. Vitamin A (retinal)



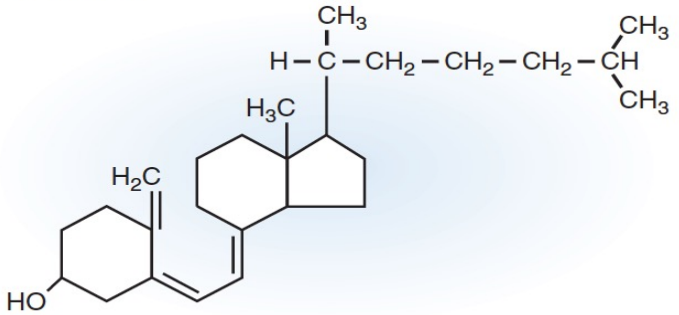
Vision
Growth
Reproduction

C. Vitamin E



Antioxidant

D. Vitamin D_3

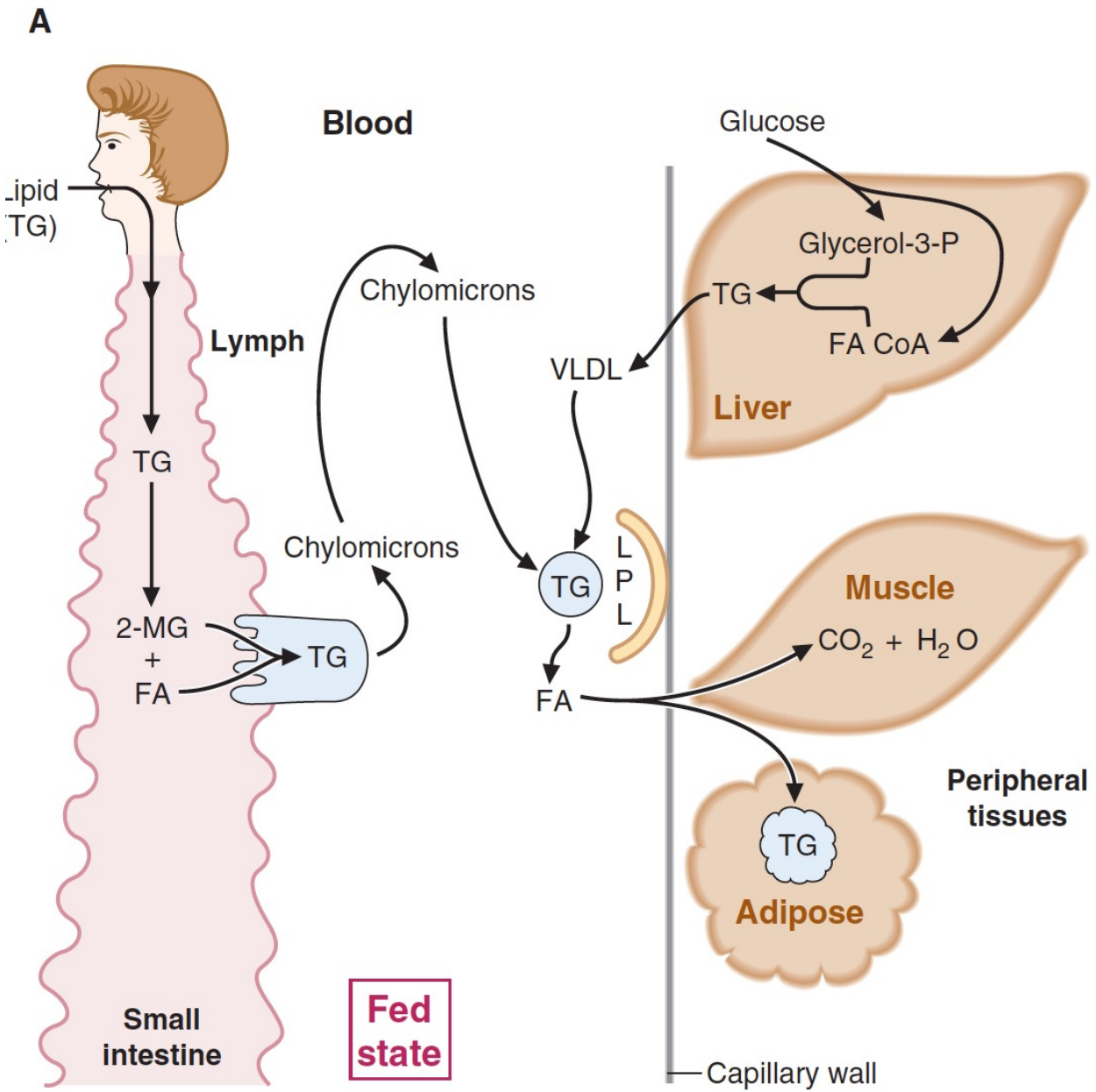


Ca^{2+} uptake from gut and mobilization from bone

FIGURE 5.7. The fat-soluble vitamins and their major functions.

LIPIDS metabolism : Fed state

- The major dietary fat is triacylglycerol, which is obtained from the fat stores of the plants and animals in the food supply.
- The dietary triacylglycerols (water-insoluble), are emulsified by bile salts and digested in the small intestine to fatty acids and 2-monoacylglycerols.
- These digestive products are resynthesized to triacylglycerols in intestinal epithelial cells and are secreted in chylomicrons via the lymph into the blood.
- Medium- and short-chain fatty acids are sufficiently soluble to pass through the intestinal epithelial cells and to enter the circulation without being incorporated into triglycerides.



FA, fatty acid; HDL, highdensity lipoprotein; LPL, lipoprotein lipase; 2-MG, 2-monoacylglycerol; TG, triacylglycerol; circled TG, triacylglycerols of VLDL and chylomicrons; VLDL, very low-density lipoprotein

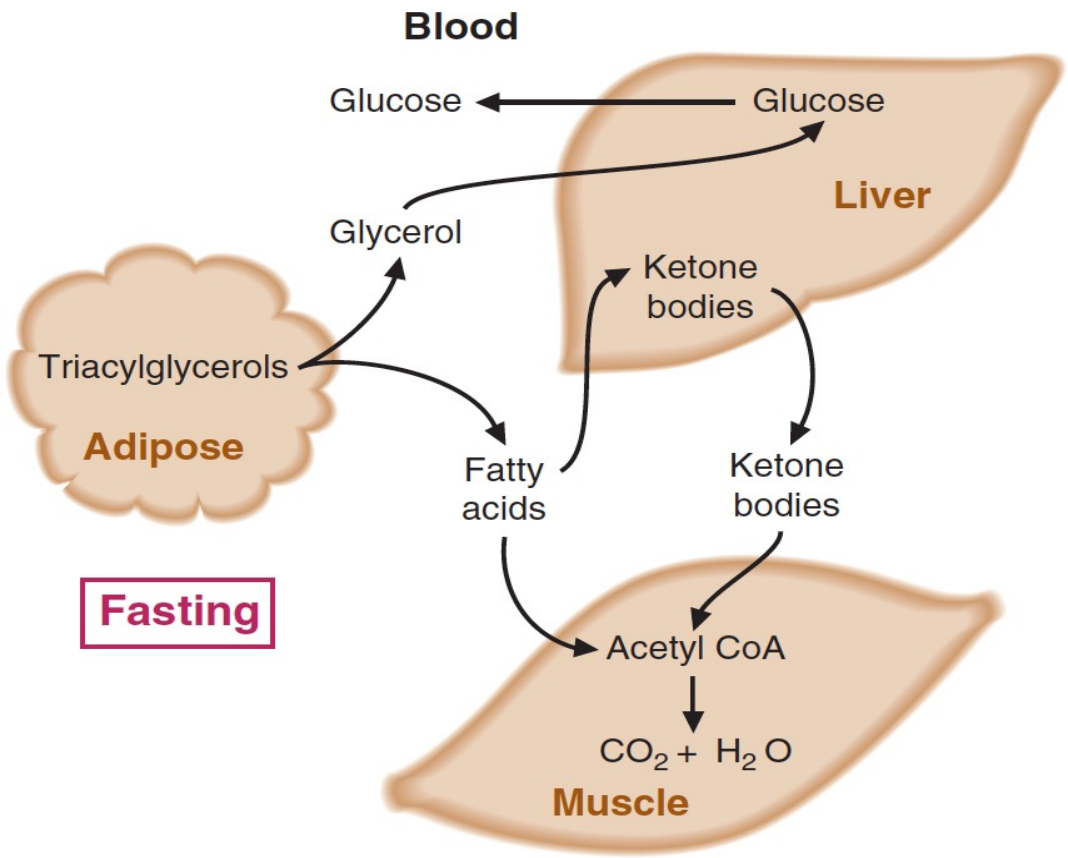
LIPIDS metabolism : Fasting state

A. Lipolysis of adipose triacylglycerols

1. In the **fasting state,** lipolysis of adipose triacylglycerols occurs.

2. Insulin levels decrease and glucagon levels rise, stimulating lipolysis. (Epinephrine and other hormones promote lipolysis by the same mechanism.)
   - ✓ cAMP levels rise, and protein kinase A is activated.
   - ✓ Protein kinase A phosphorylates and thus activates the hormone-sensitive lipase of adipose tissue.

3. The hormone-sensitive lipase initiates lipolysis, and fatty acids and glycerol are released from adipose cells.



B. Fate of fatty acids and glycerol

1. Fatty acids are:
   i. Oxidized for energy in muscle and kidney.
   ii. In the liver, fatty acids are converted to ketone bodies ➔ oxidized by tissues such as muscle and kidney. During starvation (after fasting has lasted for about 3 or more days), the brain uses ketone bodies for energy.

2. Glycerol is used by the liver as a source of carbon for gluconeogenesis, which produces glucose for brain & RBCs

Digestion of Dietary Triacylglycerols ➔ Small Intestine lumen

A. **Dietary triacylglycerols** are digested in the **small intestine** by a process that requires bile salts and pancreas enzymes

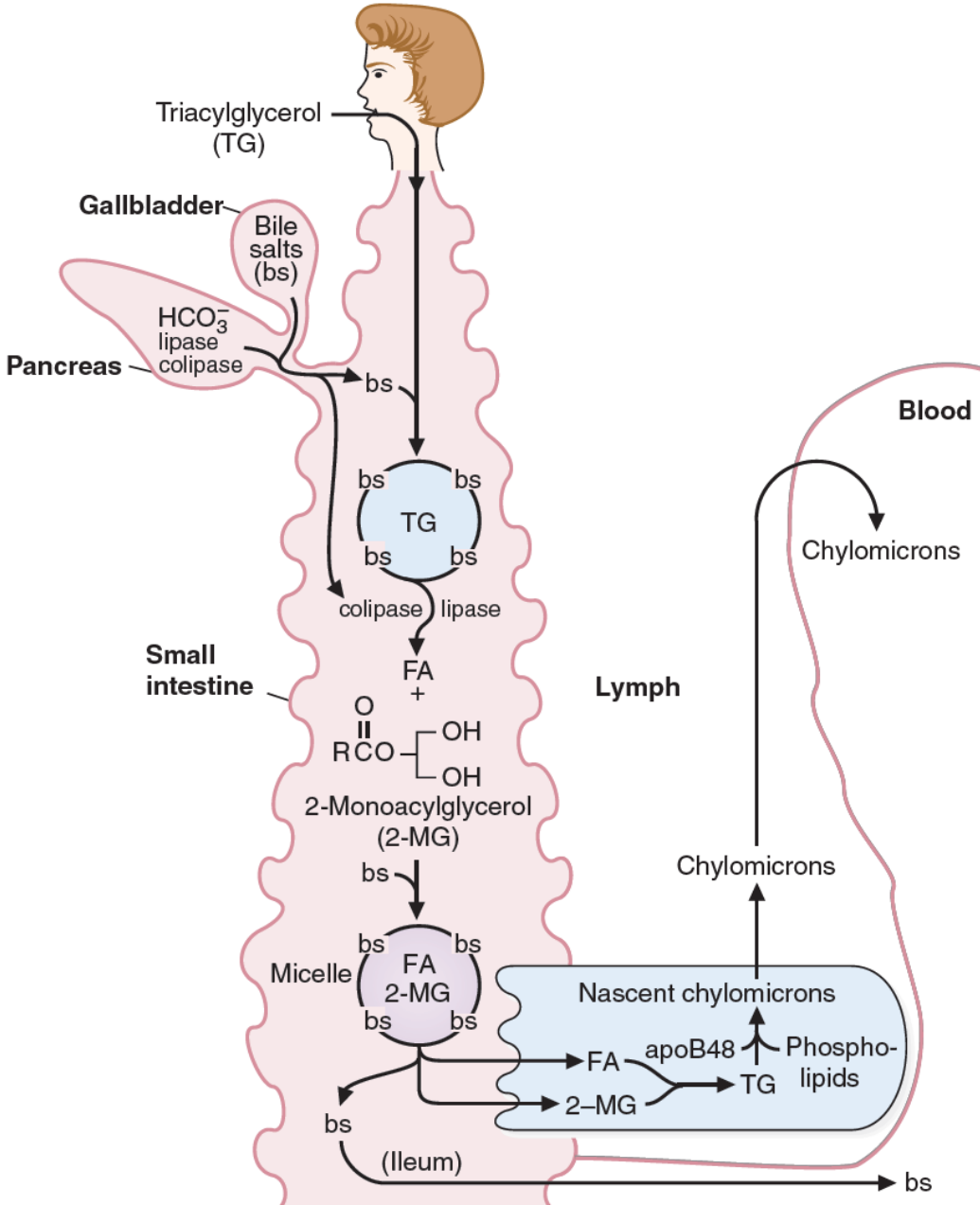
1. **Bile salts** are synthesized in the liver from cholesterol and are secreted into the bile. They pass into the intestine, where they **emulsify** the dietary lipids.

2. The **pancreas** secretes digestive enzymes and bicarbonate, which neutralizes stomach acid & raise pH

3. **Pancreatic lipase ➔ D**igests the triacylglycerols to 2-monoacylglycerols and free fatty acids, which are packaged into micelles (tiny microdroplets).

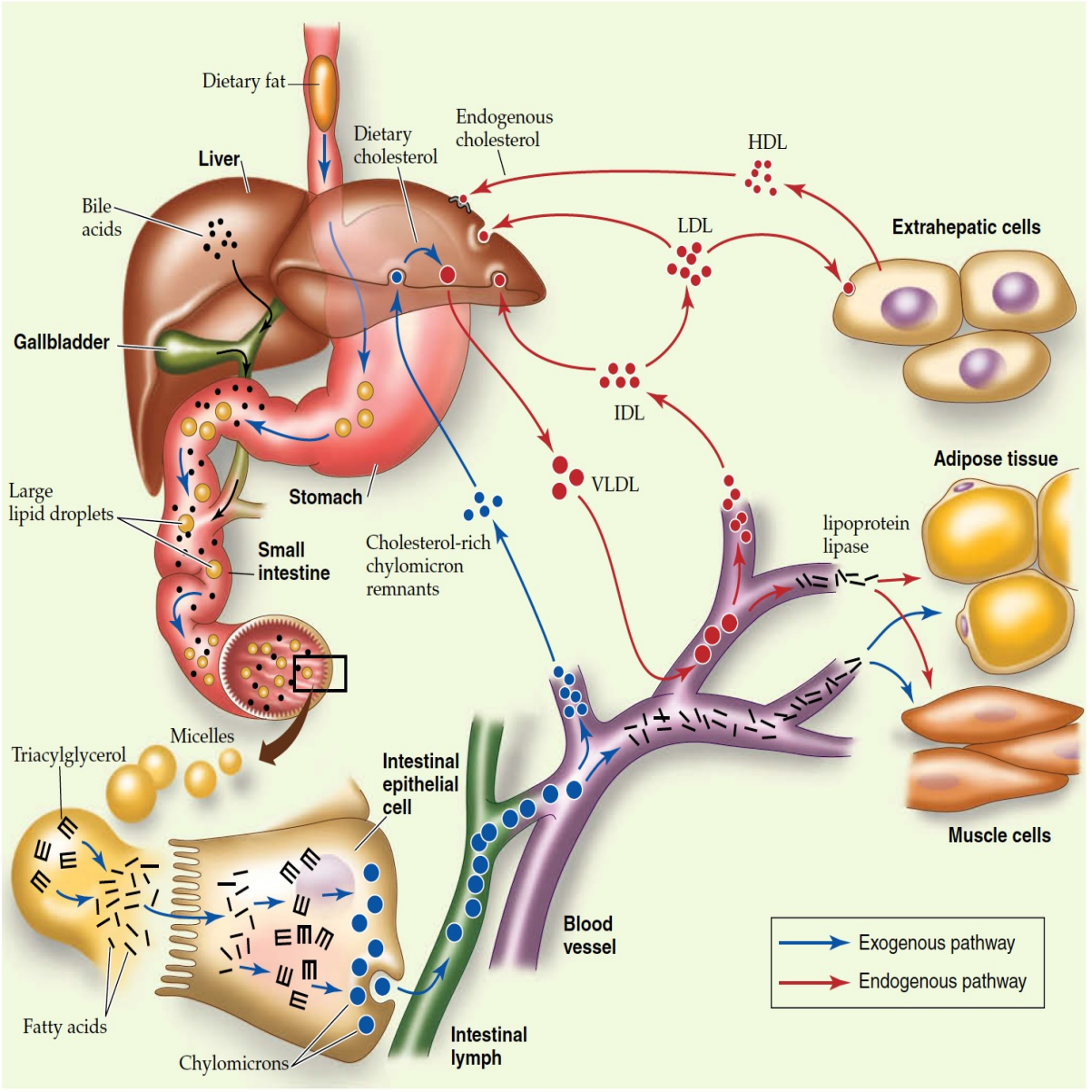
4. The **micelles** travel to the microvilli of the intestinal epithelial cells, which absorb the fatty acids, 2-monoacylglycerols, and other dietary lipids.

5. The **bile salts are resorbed,** recycled by the liver, and secreted into the gut during subsequent digestive cycles



LIPIDS Transport ➔ Blood Lipoproteins

- Chylomicrons are produced in intestinal cells from dietary lipid.
  - Chylomicron remnants are endocytosed by the liver.
- VLDL is produced in the liver, mainly from dietary carbohydrate.
- The major carriers of triacylglycerols are chylomicrons and VLDL.
- IDL consists of the remains of VLDL after digestion of some of the triacylglycerols.
  - IDL can either be endocytosed by liver cells and digested by lysosomal enzymes or
  - Converted to LDL by further digestion of triacylglycerols.
- LDL undergoes endocytosis and lysosomal digestion, both in the liver and in the peripheral tissues.
- HDL transfers proteins to chylomicrons and VLDL. HDL also picks up cholesterol from peripheral tissues and from other blood lipoproteins. This cholesterol ultimately returns to the liver. HDL transfers apoproteins, including apoC-II and apoE, to chylomicrons and VLDL
  - Cholesterol travels through the blood as a component of the lipoproteins. Cholesterol is synthesized in most cells of the body. In the liver, cholesterol is converted to **bile salts**, and it forms steroid hormones in endocrine tissues.



Composition & function of blood Lipoproteins

Lipoprotein	Density Range (g/mL)	Particle Diameter (mm) Range	Electrophoretic Mobility	Lipid (%)[a] TG	Chol	PL	Function
Chylomicrons	0.930	75–1,200	Origin	80–95	2–7	3–9	Deliver dietary lipids
Chylomicron remnants	0.930–1.006	30–80	Slow pre-β				Return dietary lipids to the liver
VLDL	0.930–1.006	30–80	Pre-β	55–80	5–15	10–20	Deliver endogenous lipids
IDL	1.006–1.019	25–35	Slow pre-β	20–50	20–40	15–25	Return endogenous lipids to the liver; precursor of LDL
LDL	1.019–1.063	18–25	β	5–15	40–50	20–25	Deliver cholesterol to cells
HDL_2	1.063–1.125	9–12	α	5–10	15–25	20–30	Reverse cholesterol transport
HDL_3	1.125–1.210	5–9	α				Reverse cholesterol transport
Lip(a)	1.050–1.120	25	Pre-β				

TG, triacylglycerols; Chol, the sum of free and esterified cholesterol; PL, phospholipid; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
[a]The remaining percent composition is composed of apoproteins.

- ✓ **Chylomicrons** are the least dense of the blood lipoproteins because they have the most triacylglycerol and the least protein.
- ✓ **VLDL** is more dense than chylomicrons but still has a high content of triacylglycerol.
- ✓ **IDL,** which is derived from VLDL, is more dense than VLDL and has less than one-half the amount of triacylglycerol.
- ✓ **LDL** has less triacylglycerol and more protein and, therefore, is more dense than the IDL from which it is derived. LDL has the highest content of cholesterol and its esters.
- ✓ **HDL** is the most dense lipoprotein. It has the lowest triacylglycerol and the highest protein content.

Function of Apoproteins

Apoprotein	Primary Tissue Source	Molecular Mass (daltons)	Lipoprotein Distribution	Metabolic Function
ApoA-I	Intestine, liver	28,016	HDL (chylomicrons)	Activates LCAT; structural component of HDL
ApoA-II	Liver	17,414	HDL (chylomicrons)	Uncertain; may regulate the transfer of apoproteins from HDL to other lipoprotein particles
ApoA-IV	Intestine	46,465	HDL (chylomicrons)	Uncertain; may be involved in the assembly of HDL and chylomicrons
ApoB-48	Intestine	264,000	Chylomicrons	Assembly and secretion of chylomicrons from small bowel
ApoB-100	Liver	540,000	VLDL, IDL, LDL	VLDL assembly and secretion; structural protein of VLDL, IDL, and LDL; ligand for LDL receptor
ApoC-I	Liver	6,630	Chylomicrons, VLDL, IDL, HDL	Unknown; may inhibit the hepatic uptake of chylomicron and VLDL remnants
ApoC-II	Liver	8,900	Chylomicrons, VLDL, IDL, HDL	Cofactor activator of lipoprotein lipase (LPL)
ApoC-III	Liver	8,800	Chylomicrons, VLDL, IDL, HDL	Inhibitor of LPL; may inhibit the hepatic uptake of chylomicrons and VLDL remnants
ApoE	Liver	34,145	Chylomicron remnants, VLDL, IDL, HDL	Ligand for binding of several lipoproteins to the LDL receptor, to the LDL receptor–related protein (LRP), and possibly to a separate apoE receptor
Apo(a)	Liver		Lipoprotein "little" a (Lp(a))	Unknown; consists of apoB-100 linked by a disulfide bond to apoprotein (a)

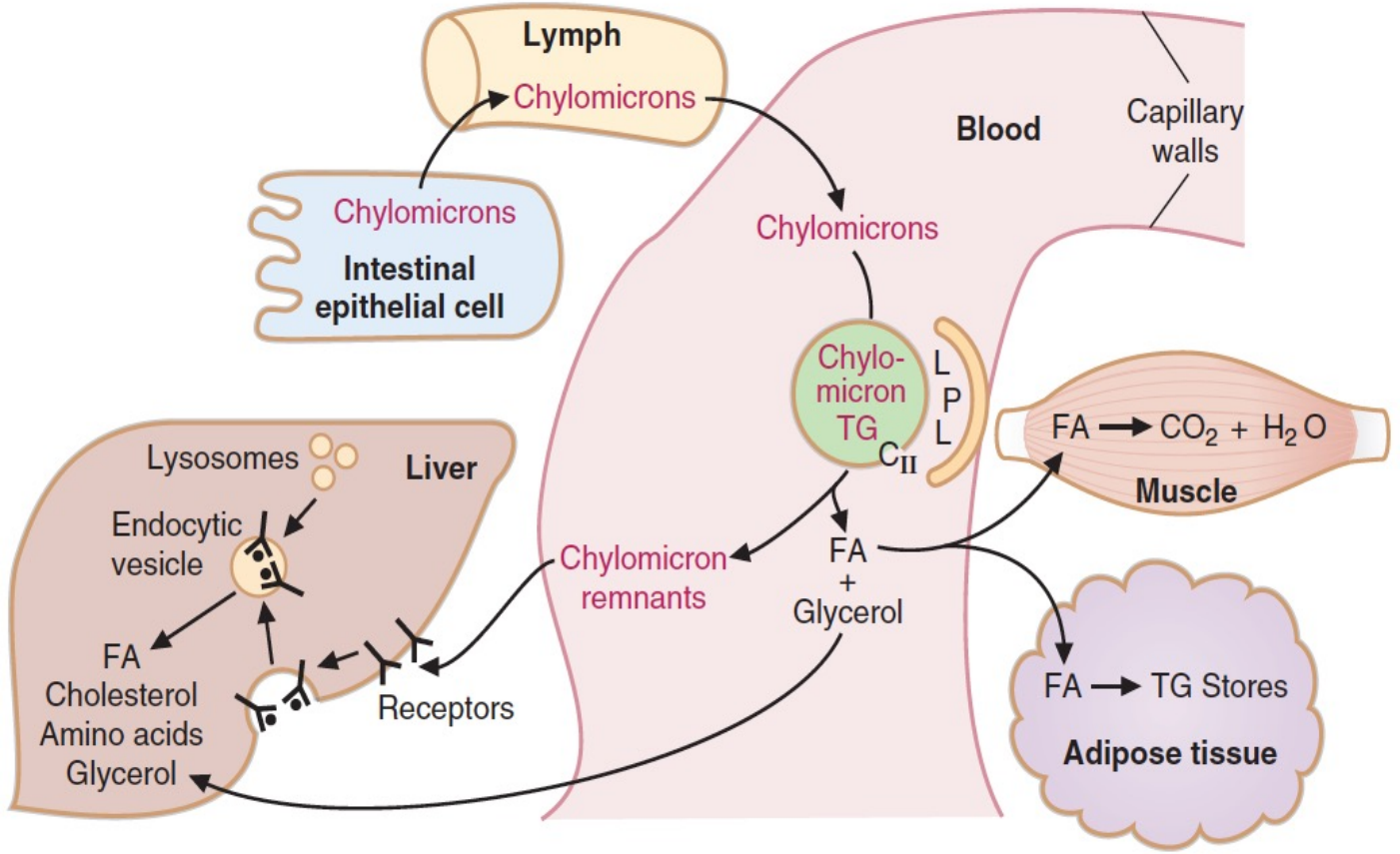
Metabolism of Chylomicrons

1. Chylomicrons are synthesized in intestinal epithelial cells. Their triacylglycerols are derived from dietary lipid, and their major apoprotein is apoB-48.

2. Chylomicrons **travel through the lymph** into the **blood**. ApoC-II, the activator of lipoprotein lipase, and **apoE** are transferred to nascent chylomicrons from **HDL**, and mature chylomicrons are formed.

3. In peripheral tissues, particularly adipose and muscle, the triacylglycerols are digested by **lipoprotein lipase.**

4. The chylomicron remnants interact with the receptors on liver cells and are taken up by endocytosis. The contents are degraded by lysosomal enzymes, and the products (amino acids, fatty acids, glycerol, cholesterol, and phosphate) are released into the cytosol and reutilized.



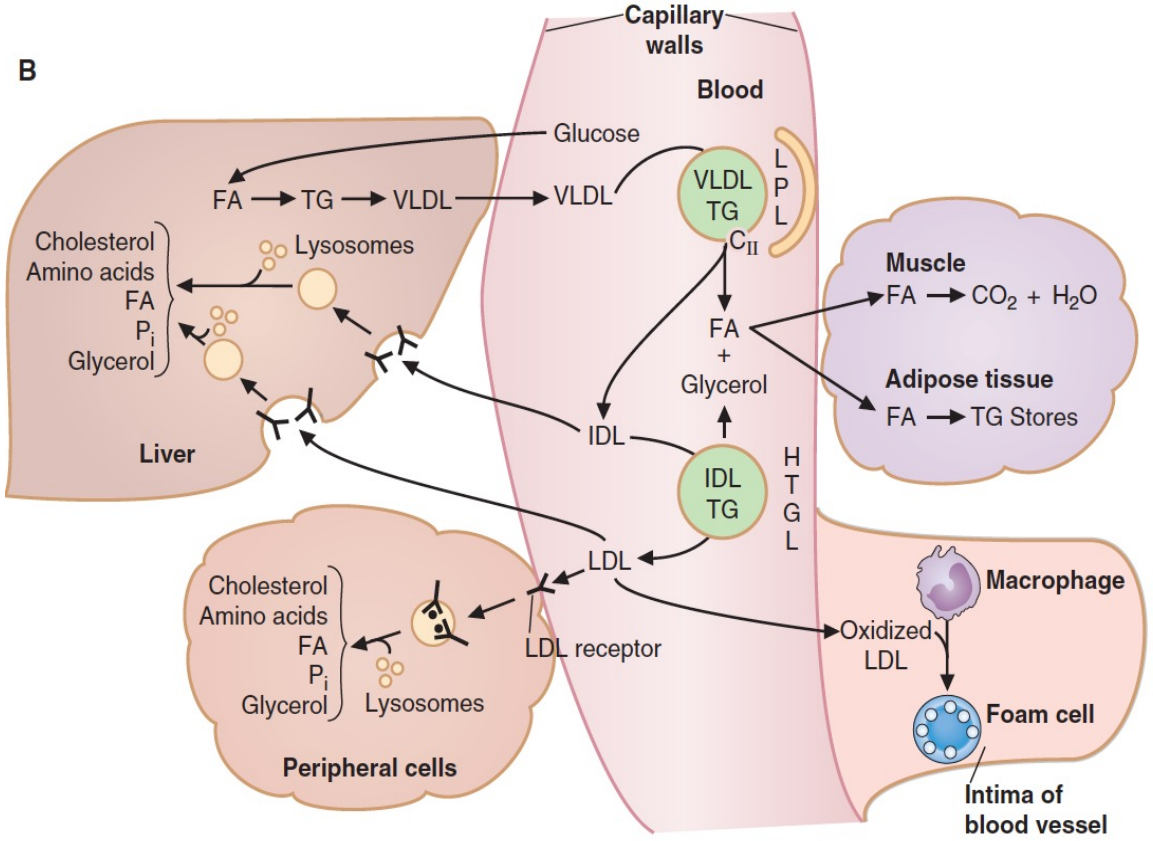
Metabolism of VLDL

1. VLDL is synthesized in the liver, particularly after a high-carbohydrate meal. It is formed from triacylglycerols that are packaged with cholesterol, apoproteins (particularly apoB-100), and phospholipids, and it is released into the blood.

2. In peripheral tissues, particularly adipose and muscle, VLDL TAGs are digested by lipoprotein lipase, and VLDL is converted to IDL.

3. IDL returns to the liver, is taken up by endocytosis, and is degraded by lysosomal enzymes to LDL.

4. LDL reacts with the receptors on various cells, is taken up by endocytosis, and is digested by lysosomal enzymes.
   i. Cholesterol, released from cholesterol esters by a lysosomal esterase, is used for the synthesis of membranes or synthesis of bile salts (liver) or steroid hormones (endocrine tissue).
   ii. Cholesterol inhibits HMG-CoA reductase and, thus, decreases the rate of cholesterol synthesis by the cell.
   iii. Cholesterol inhibits the synthesis of LDL receptors (downregulation), and, thus, reduces the amount of cholesterol taken up by cells.
   iv. Cholesterol activates acyl:cholesterol acyltransferase (ACAT), which converts cholesterol to cholesterol esters for storage in cells.



Metabolism of HDL

1. HDL is synthesized by the liver and released into the blood *as small, disk-shaped particles*. The major protein of HDL is **apoA.**

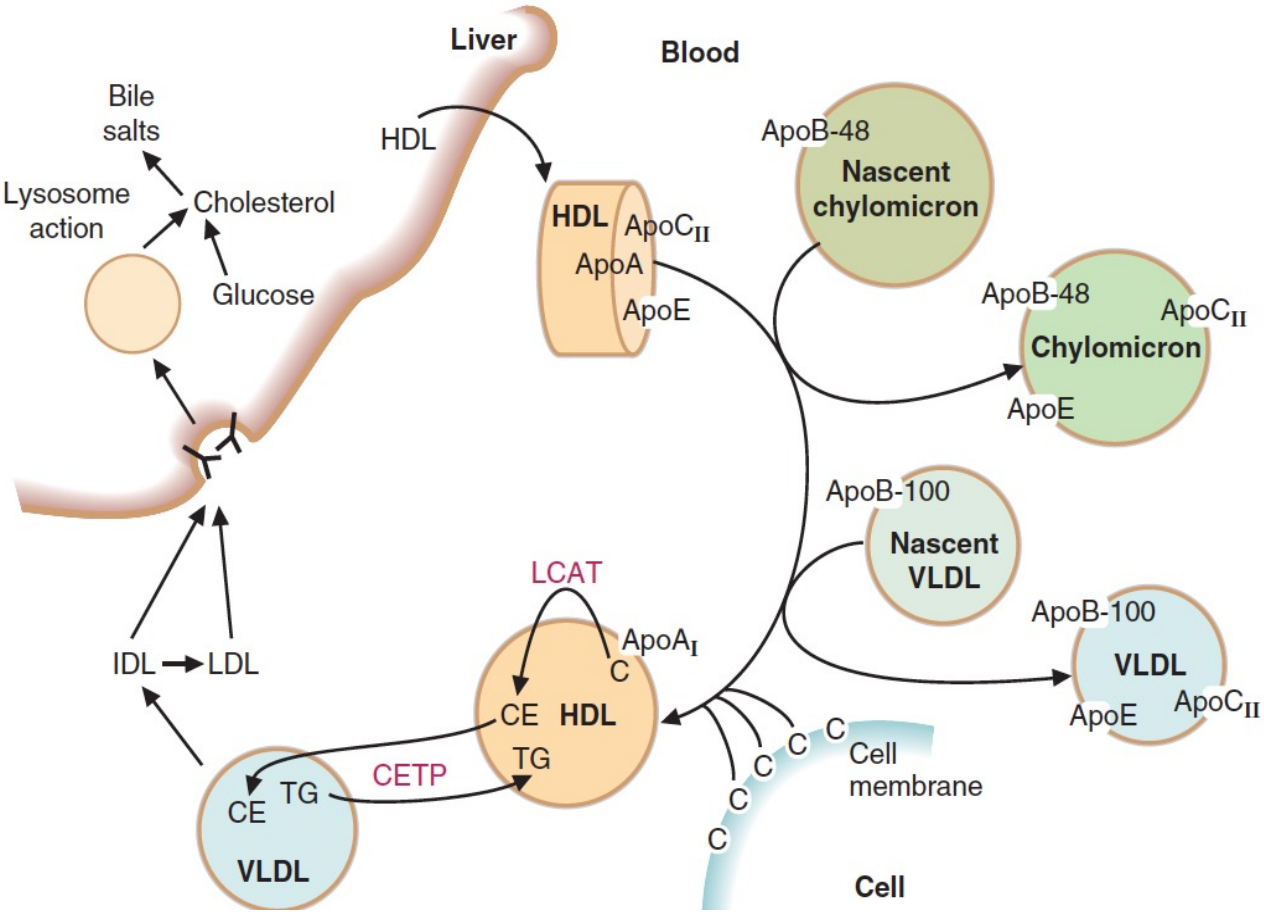
2. **ApoC-II**, which is transferred by HDL to chylomicrons and VLDL, serves as an activator of lipoprotein lipase. ApoE is also transferred and serves as a recognition factor for cell surface receptors. ApoC-II and apoE are transferred back to HDL following the digestion of triacylglycerols of chylomicrons and VLDL.

3. Cholesterol, obtained by HDL from the cell membranes or from other lipoproteins, is converted to cholesterol esters by the LCAT reaction, which is activated by apoAI. As cholesterol esters accumulate in the core of the lipoprotein, HDL particles *become spheroids.*

4. **HDL transfers cholesterol esters** to other lipoproteins in exchange for various lipids. **HDL and other lipoproteins carry the cholesterol esters back to the liver.**

5. HDL particles and other lipoproteins are **taken up by the liver** by endocytosis and hydrolyzed by lysosomal enzymes.

6. Cholesterol, released from cholesterol esters, can be packaged by the liver in VLDL and released into the blood or converted to bile salts and secreted into the bile.



Questions