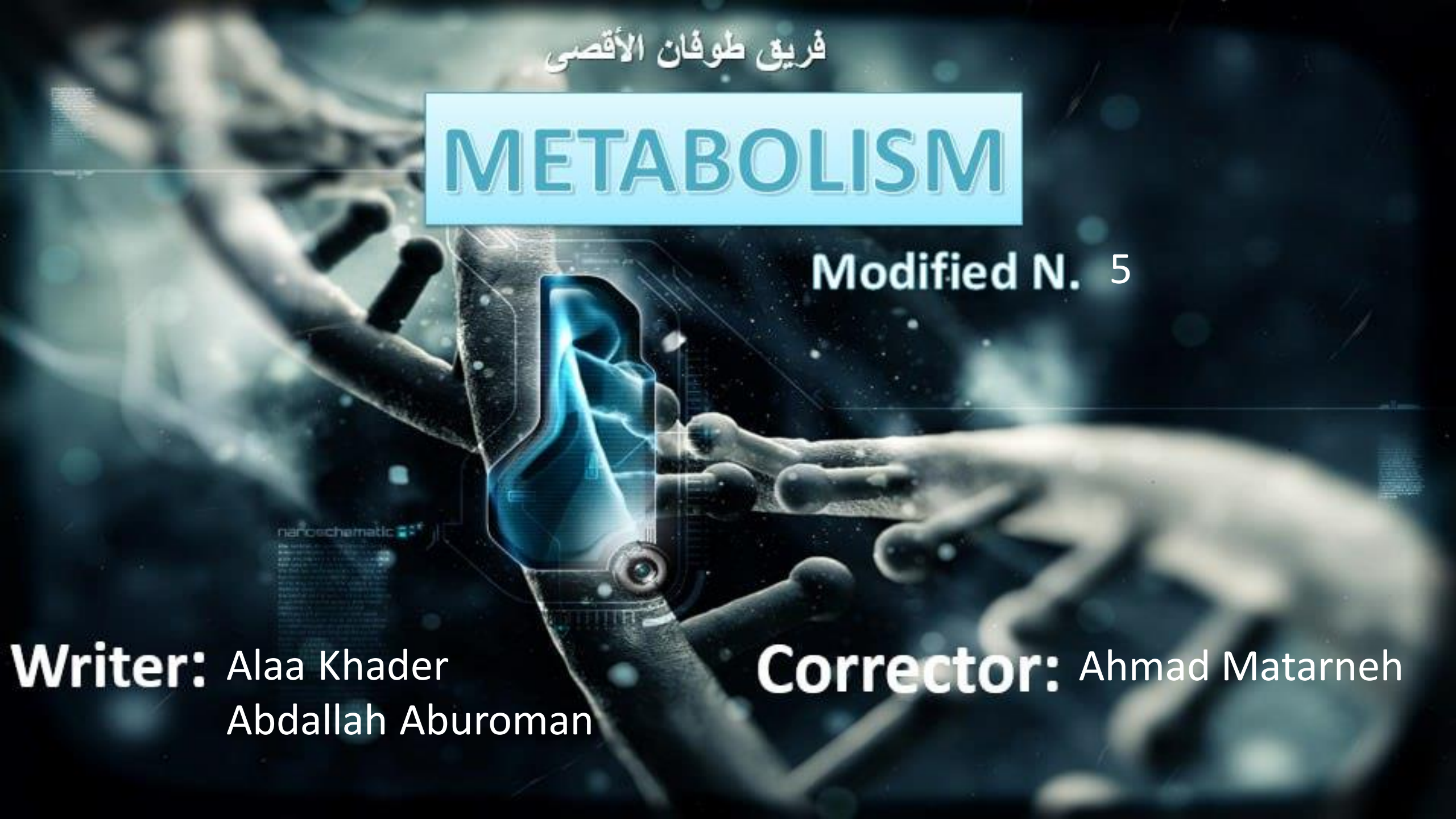
فريق طوفان الأقصى

METABOLISM

Modified N. 5



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Resources

This lecture

Lippincott's Biochemistry, Ch. 15

Metabolism of lipids I:

Absorption and transport

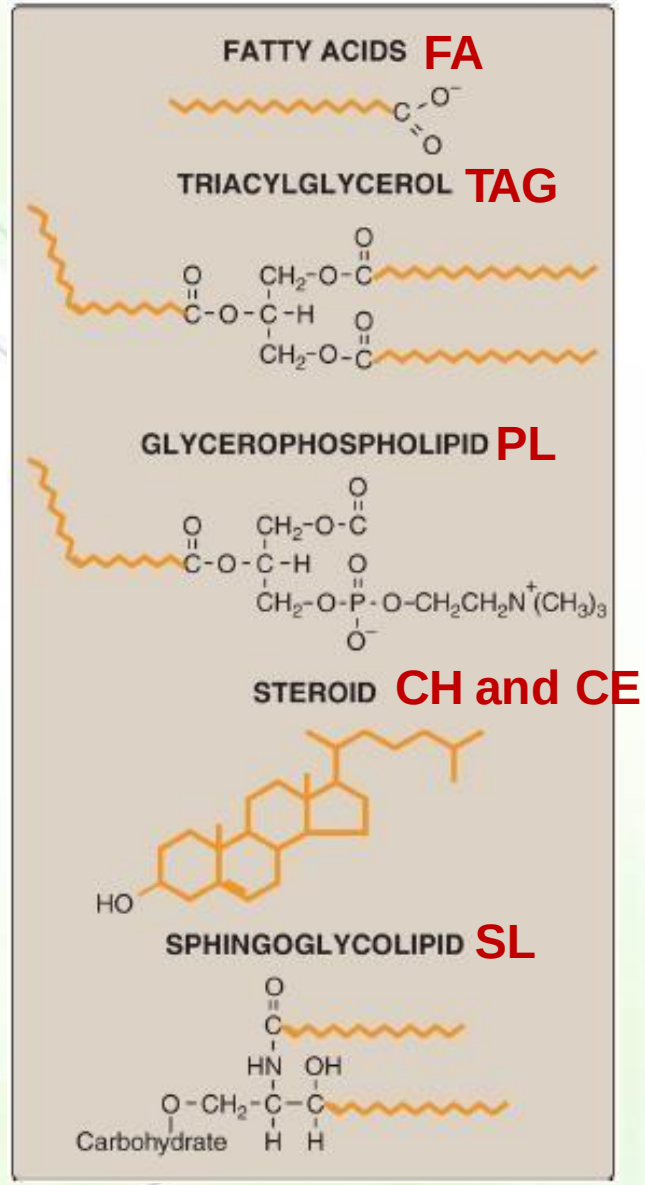
Prof. Mamoun Ahram

What are lipids?

NOTE: !! Watch the lecture !!

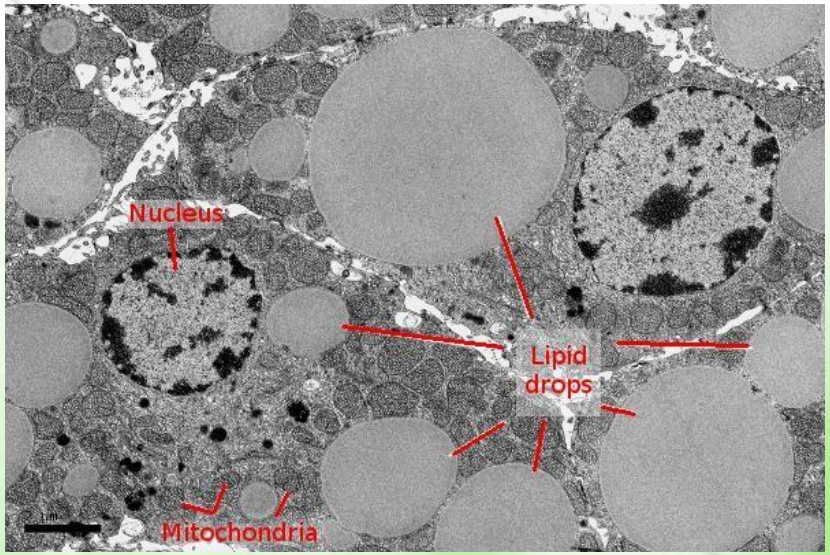
- Lipids are heterogeneous, hydrophobic (not polymers) , compartmentalized in membranes, as droplets of triacylglycerol (TAG) (the majority of lipids (90%) are in this form), or in lipoprotein (LP) particles, or protein-bound.
- Functions: Energy (ATP), structures, molecular precursors (e.g., vitamins, signaling, hormones)

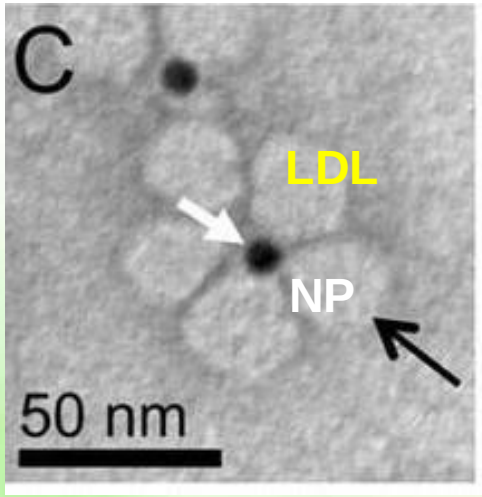
The major dietary lipids are triacylglycerol, cholesterol, and phospholipids.



- To refresh your memory, there are four types of macromolecules: carbohydrates, proteins, nucleic acids and lipids. Lipids are the only macromolecules that are not polymers (that is, they do not consist of same repetitive monomers)
- **FUNCTIONS:** The main function of lipids is the production of energy ATP Mainly ,structural molecule (eg: plasma membrane of organelles, cell), signaling molecules (phosphatidyl inositol its is a signaling molecule in cells)

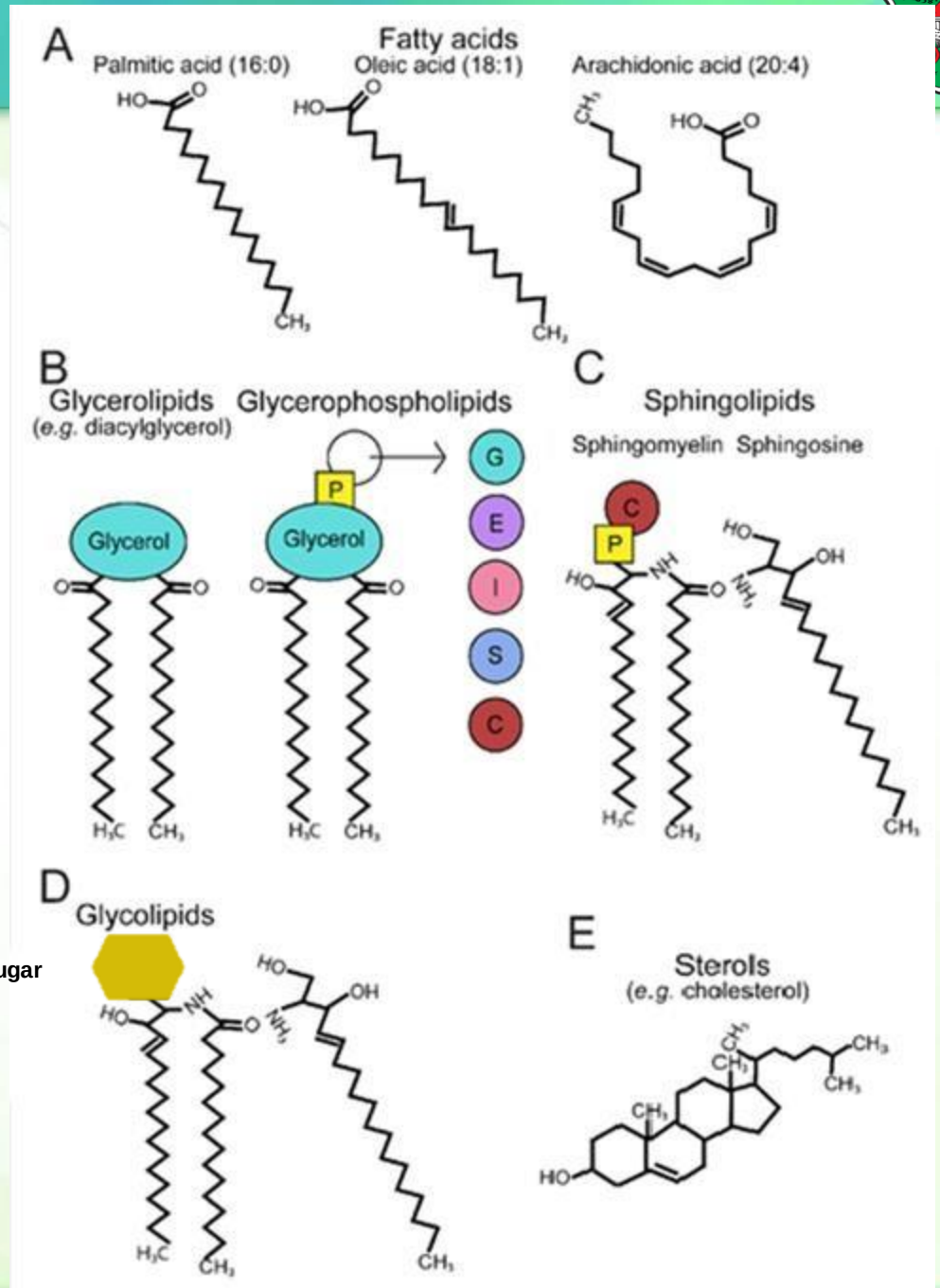
- **The complement in this slide:** these are electron microscopic images
- **On the left:** it is in adipocyte cell, we have lipid drops, as you can see, they aggregate and cluster.
- **On the right:** they are droplets (smaller) **LDL** surrounded by a nano particle **NP**

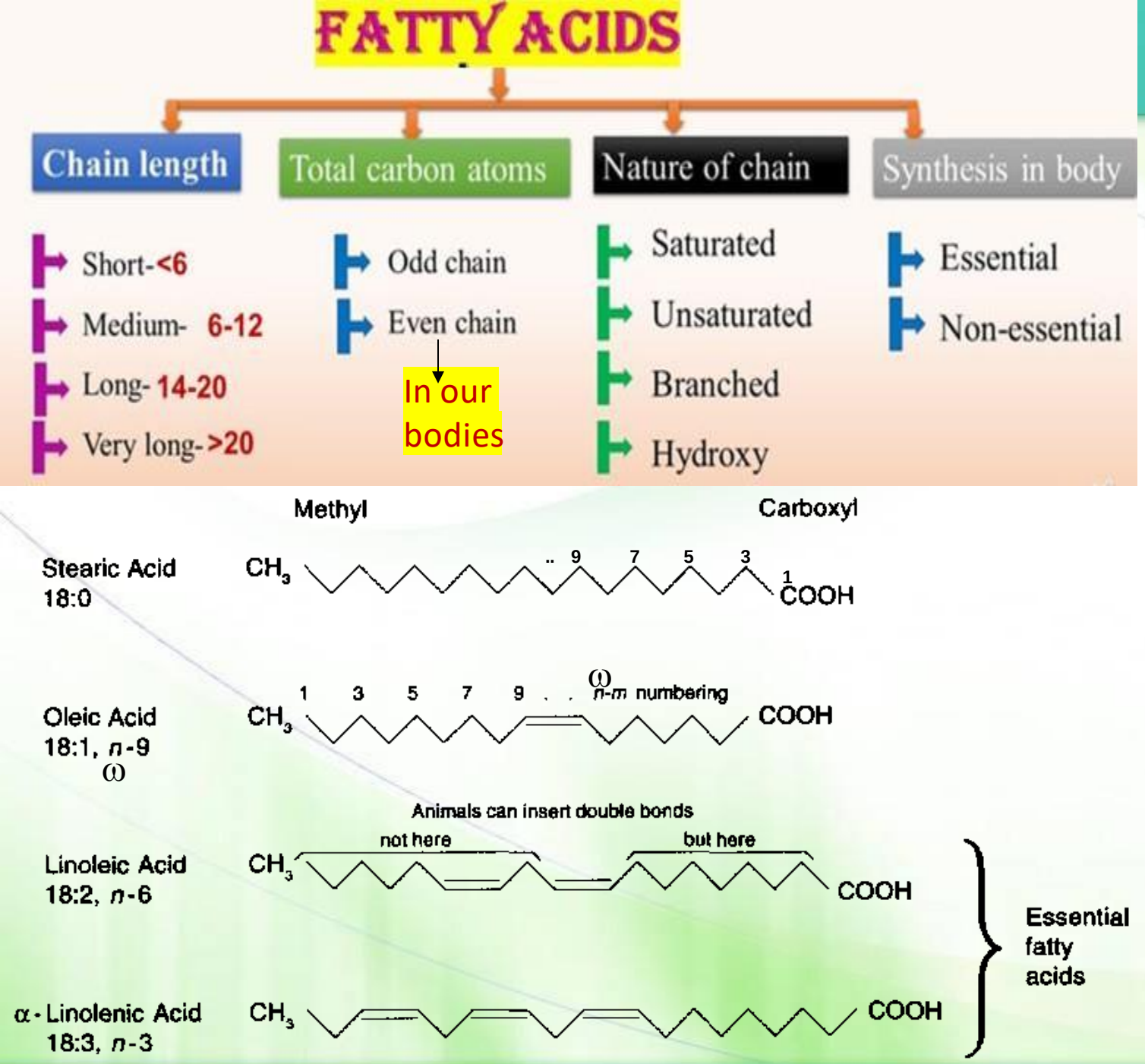




Structure and classification of lipids

- **NOTE:** refresh memory (we took in biochem1)
- **A)** we have fatty acids (FA) which can be **saturated** (no double bonds) or **unsaturated** (double bonds), that can be mono-unsaturated or poly-unsaturated
- **B) Glycerolipids:** Glycerol (backbone) + 1,2,or 3 FA(fatty acids)→(mono/di/triacylglycerols) respectively. We can also add a **phosphate** group → **phospholipid**, also we can add head group on this phosphate group.
- **C) sphingolipid:** Sphingosine +phosphocholine= sphingomyelin (only sphingo- phospholipid)
- **D) Glycolipid:** Sphingosine + sugar
- **E) Steroids:** cholesterol and its derivatives (sex hormones, cortisol)





- Double bonds (**unsaturation**) in FA are always spaced at three-carbon intervals.
- The addition of **double bonds** decreases the melting temperature (Tm) of a fatty acid.
  - *But increasing the chain's length increases the Tm.*
- Membrane lipids typically contain unsaturated long-chain fatty acids (LCFA) to maintain fluidity.
- Fatty acids with double bonds beyond the 10th carbon are essential.

- **NOTES in the CLASSIFICATION:** SCFA(short chain fatty acid), MCFA(Medium chain fatty acid), LCFA(Long chain fatty acid).**You need to know the abbreviations**

- **Essential fatty acids: linoleic acid** (omega 6) and **linolenic acid** (omega 3) are called omega carbons depending on the first double bonds relative to the CH_3

- **The complement in this slide:**
- **IF we increase the double bonds → increase fluidity and decrease T_M (melting point)**

- **The Reason why these FAs are essential because our body doesn't have enzymes that "can introduce double bonds beyond 10^{th} Carbon". (numbering from carboxylic group)**

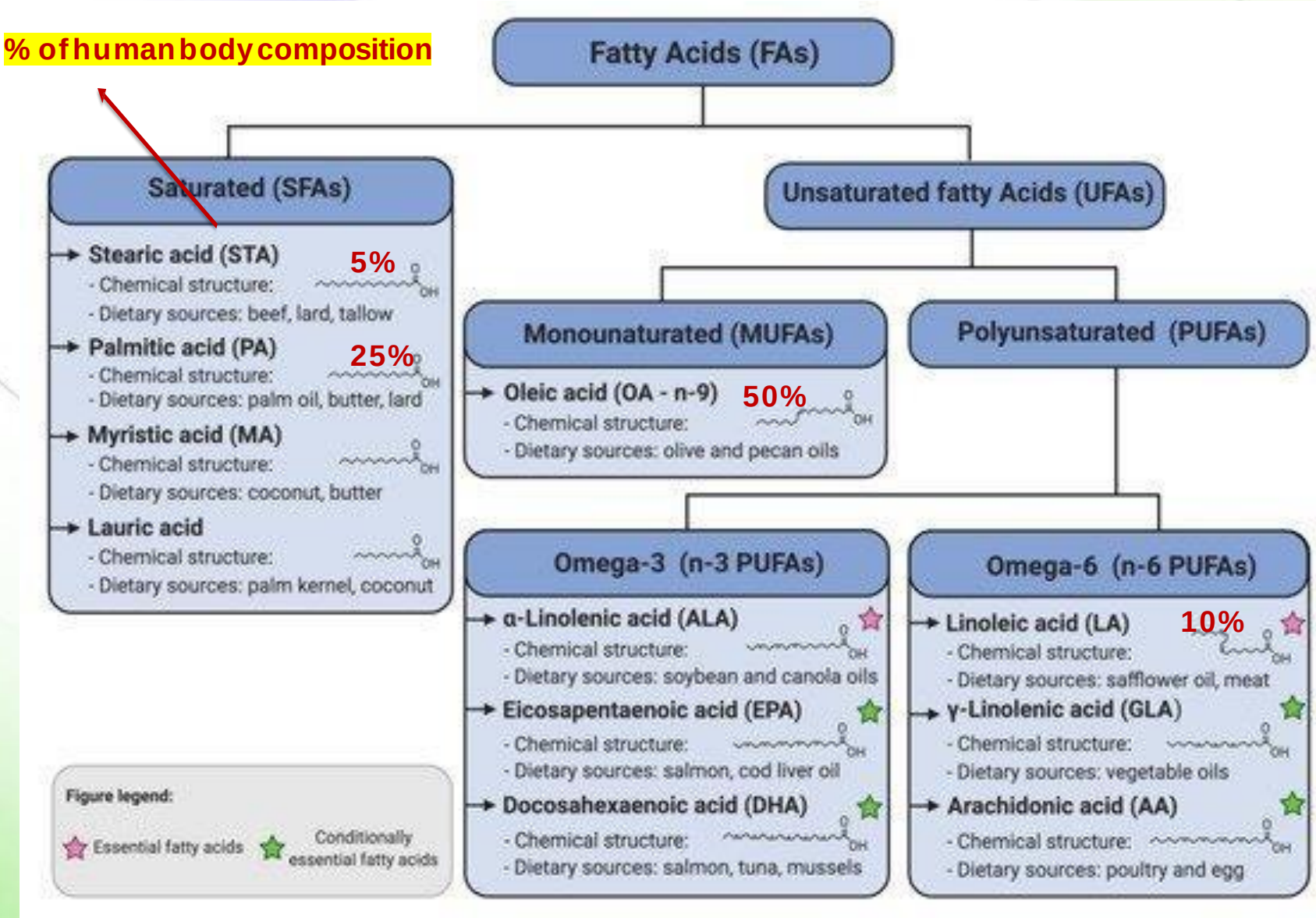
- **Additional information: to know the relation between Tm and double bonds (cytology slides)**

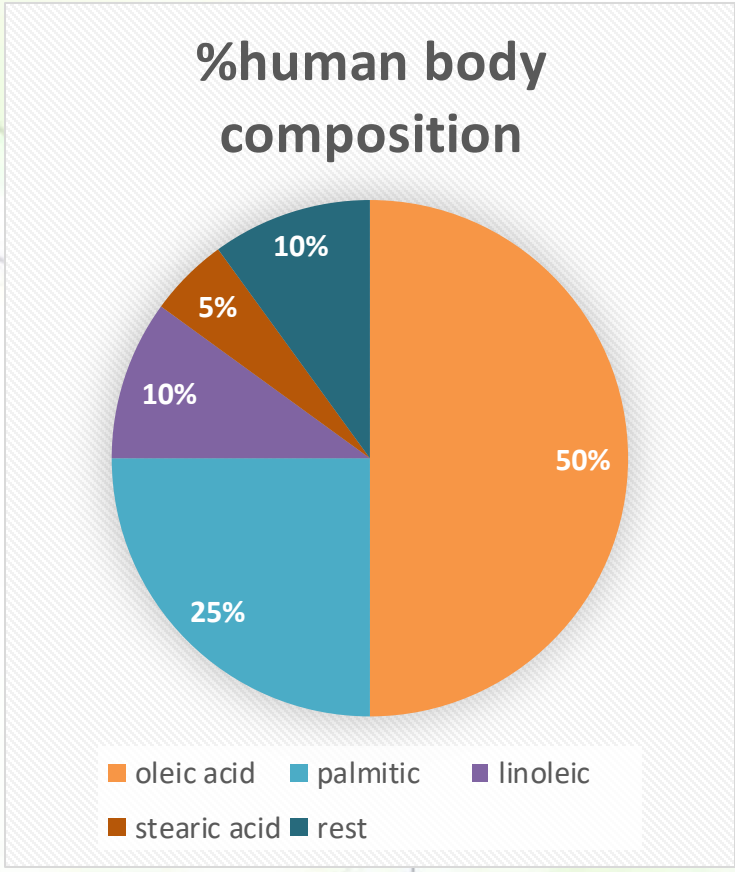
TABLE 4.2 Melting Points of the Common 18-Carbon Fatty Acids

Fatty acid	*cis* Double bonds	M.p. (°C)
Stearic acid	0	70
Oleic acid	1	13
Linoleic acid	2	−9
Linolenic acid	3	−17
Eicosapentanoic acid (EPA)*	5	−54

*EPA has 20 carbons.

% of human body composition





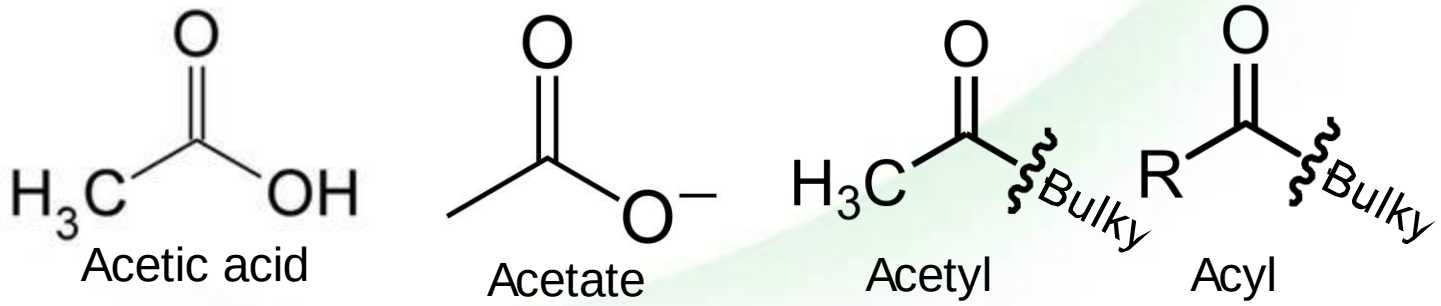
Forms of fatty acids

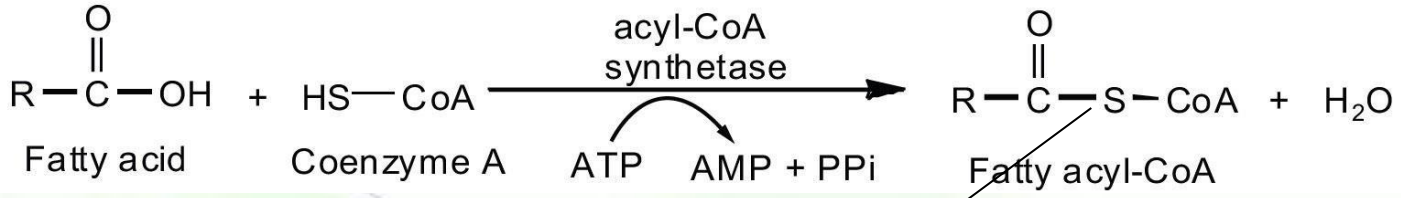
- Free fatty acids (FFA): occur in all tissues and in plasma (particularly during fasting).
  - >90% of the plasma fatty acids are in the form of fatty acid esters (primarily TAG, cholesteryl esters, and phospholipids) carried by circulating lipoprotein particles. Plasma
  - FFA are transported on albumin from adipose tissue to most tissues.
- FFA can be oxidized (broken up into acetyl CoA) in many tissues:
  - Liver and muscle, to provide energy
  - Liver to synthesize ketone body. Acetyl CoA→ ketone bodies
- Structural FA: membrane lipids as phospholipids and glycolipids
- Protein-associated FAs facilitate (plasma) membrane attachment.
- FAs are precursors of the hormone-like prostaglandins
- Esterified FAs: in the form of TAG stored in white adipose tissues as the major energy reserve of the body.

- **The complement in this slide:** In our cells in general, we don't have fatty acid in the free form, they are associated with other compounds like **cholesterol** (cholesteryl esters) which are very hydrophobic, **glycerol** (triacylglycerols) ,**phospholipids** (plasma membrane) ,**lipoproteins** like chylomicrons , LDL , HDL and by **Albumin**

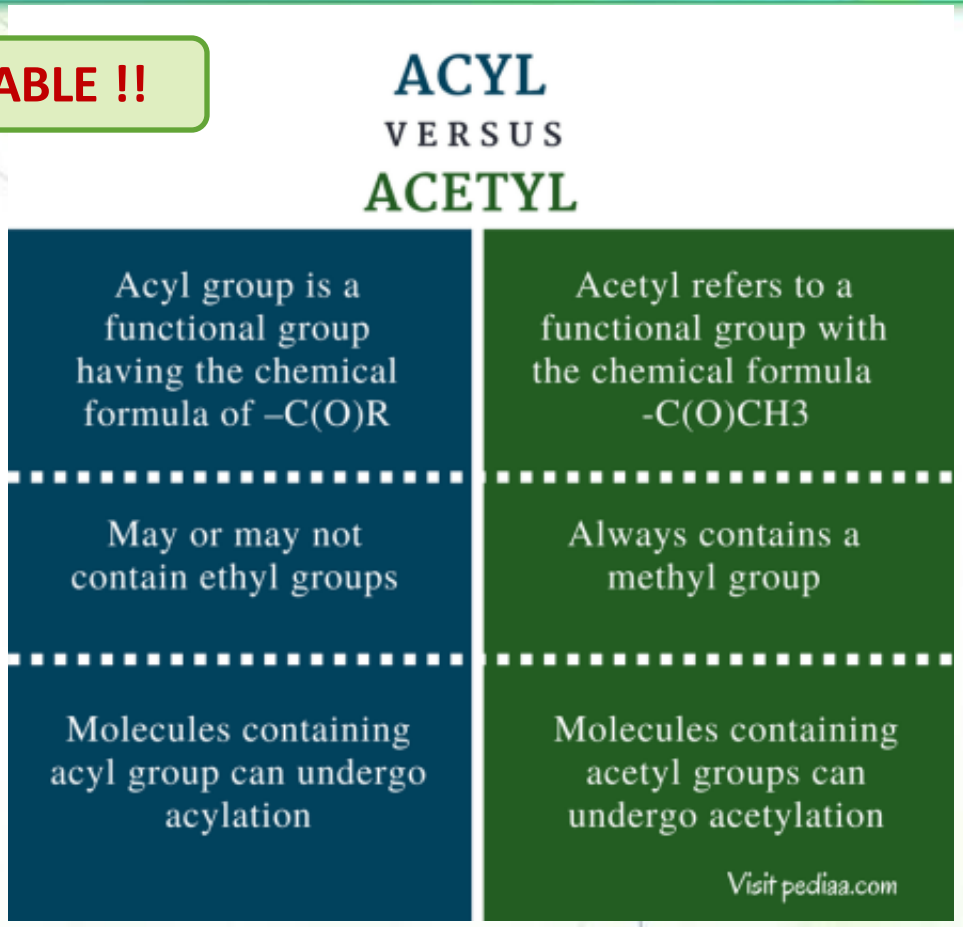
Acetyl versus acyl

NOTE: READ THE TABLE !!



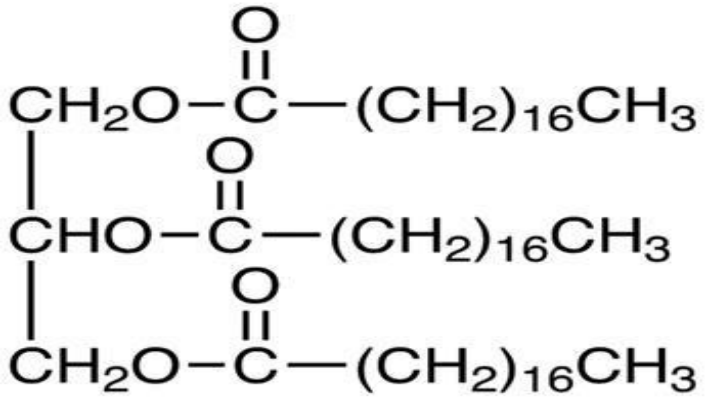


NOTE: Any molecule with CoA is a high energy molecule, and the bond between acyl group & CoA is a high energy bond.
remember that

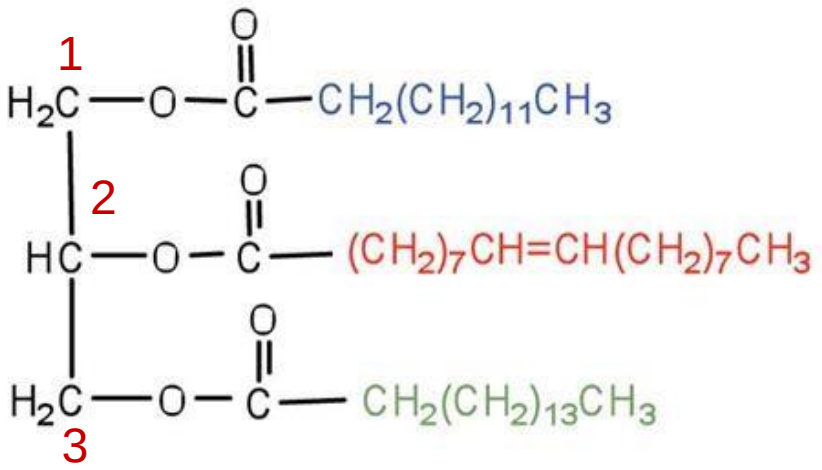


Both groups are composed of alkyl groups (R) along with another group (CoA).

Triacylglycerol



Tristearin
a simple triglyceride

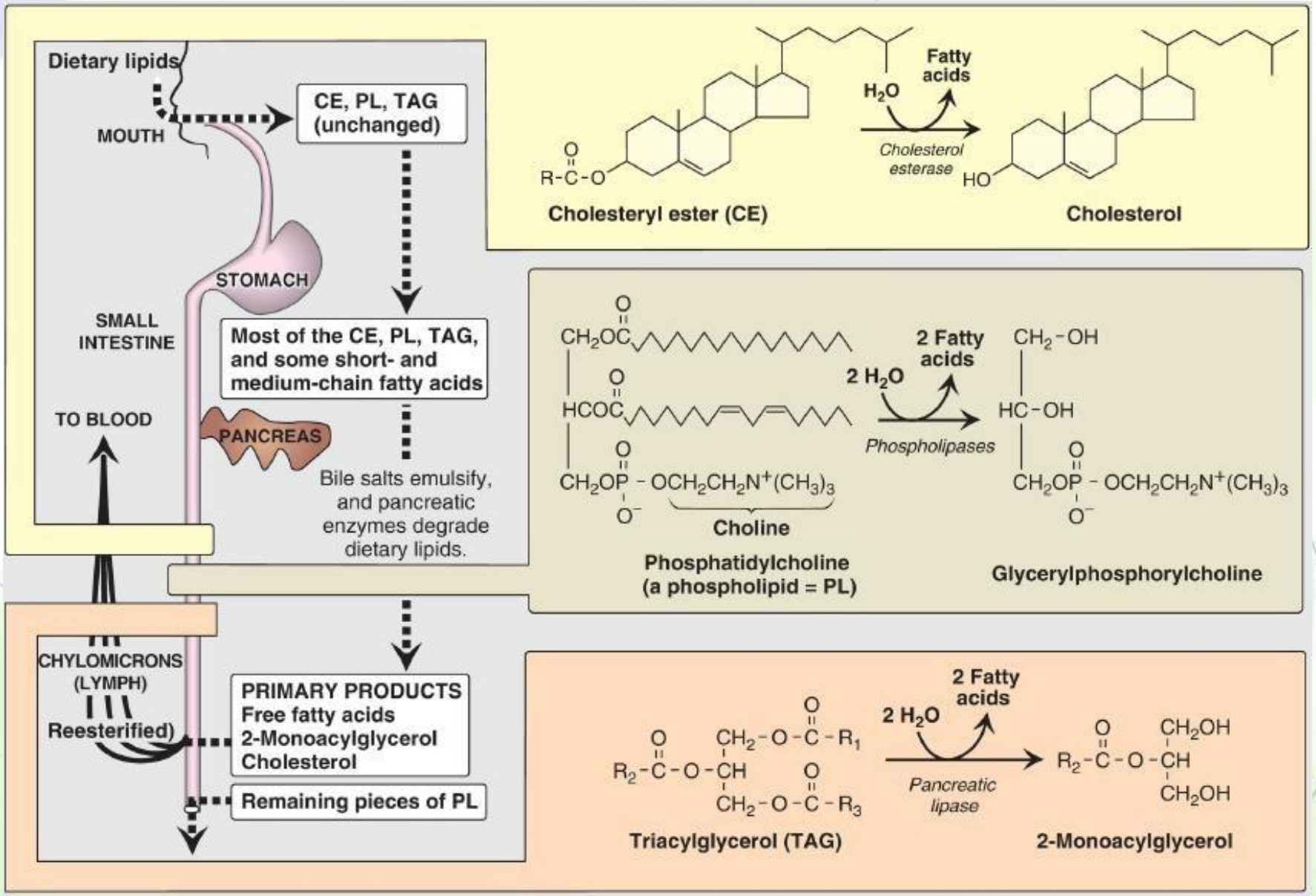


a mixed triglyceride

Usually, polyunsaturated FAs

- **NOTE:** Mainly, 3 fatty acids are linked (by **ester bond**) to **glycerol** forming triacylglycerol.
- If these 3 fatty acids were **identical** -> simple triglyceride
- **Different** -> mixed triglyceride
- Usually, FA in 2nd carbon in our body is **poly-unsaturated**; it increases fluidity of the molecule.

Digestion of lipids



- **The complement in this slide:** Digestion of lipids starts its journey in the **mouth**, then it continues in the **stomach** where some of it gets absorbed. The remaining goes into the **intestines**, which are the **main site** of lipid digestion, as they have the necessary enzymes to digest and break lipids.
- The 3 main enzymes are: **cholesterol lipase** (breaks FAs linked to cholesterol), **pancreatic lipases** (break down triacylglycerol linked lipids), **phospholipases** (break down FAs linked to phospholipids, specifically carbons 1 and 2)
- **Mouth** : lipids are first broken down by an enzyme called **lingual lipase**, لكنه ما بلحق يشتغل but it is an **acid stable** enzyme, so it survives in the stomach and continues its digestion there.
- **Stomach**: we have another acid stable digestion enzyme in the stomach called **gastric lipase**, both lingual and gastric lipases act on the **short & medium length FA**. The released FAs can be absorbed → enter circulation. (binding to **albumin** and carried to tissues)
- **Intestine**: Pancreatic lipases will act, and they are responsible for the majority digestion of TAGs and releasing most of FAs.
- **NOTE:** People with pancreatic lipase **deficiency**, they rely on short and medium chain fatty acids diet; because they can't degrade LONG FAs.

Digestion in the stomach

- Acid-stable lipases: lingual lipase and gastric lipase
- They have an optimum pH of 2.5 – 5.
- Main target: triacylglycerols with short- and medium-chain fatty acids (≤ 12 carbons)
- Significant in infants and patients with pancreatic lipase deficiency or pancreatic insufficiency (e.g., cystic fibrosis).
  - The action of lingual lipase is significant in newborn infants.
- Short- and medium-chain fatty are absorbed in the stomach.

Fatty acids	*Human milk*[a] *%*
4:0	—
6:0	—
8:0	0.16
10:0	1.82
10:1 + 11:0	—
12:0	7.89
13:0	—
14:0	9.45
14:1 + 15:0 + 15:1	0.84
16:0	22.78
16:1 + 17:0 + 17:1	3.04
18:0	6.51
18:1 (*n*-9)	28.72
18:2 (*n*-6)	15.12
18:3 (*n*-6)	0.15
18:3 (*n*-3)	0.82
20:0	0.40
20:1	0.21
20:2	0.31
20:3 (*n*-6)	0.53
20:4 (*n*-6)	0.52
20:5 (*n*-3)	0.10
22:0	—
22:1	—
22:4 (*n*-6)	0.08
22:5 (*n*-6)	0.01
22:5 (*n*-3)	0.17
22:6 (*n*-3)	0.32
24:0	0.04

Wet nursing

Ozkan *et al. Clinical Epigenetics* 2012, **4**:14
http://www.clinicalepigeneticsjournal.com/content/4/1/14

CLINICAL EPIGENETICS

HYPOTHESIS Open Access

Milk kinship hypothesis in light of epigenetic knowledge

Hasan Ozkan*, Funda Tuzun, Abdullah Kumral and Nuray Duman

RESEARCH ARTICLE

Breastfeeding effects on DNA methylation in the offspring: A systematic literature review

Fernando Pires Hartwig[1,2]*, Christian Loret de Mola[1], Neil Martin Davies[2,3], Cesar Gomes Victora[1], Caroline L. Relton[2,3]

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Irmak *et al. Theoretical Biology and Medical Modelling* 2012, **9**:20
http://www.tbiomed.com/content/9/1/20

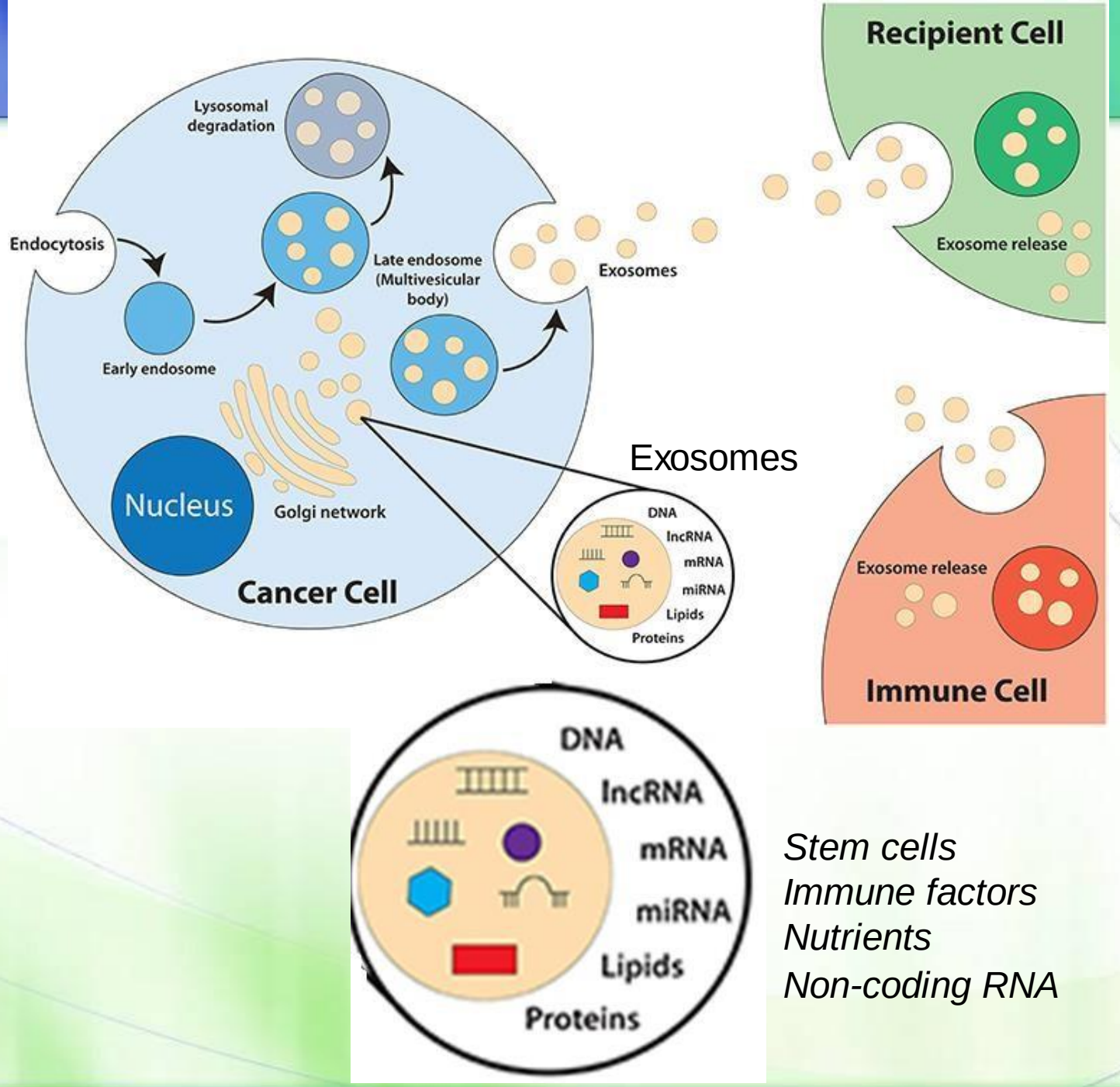
THEORETICAL BIOLOGY AND MEDICAL MODELLING

REVIEW Open Access

Integration of maternal genome into the neonate genome through breast milk mRNA transcripts and reverse transcriptase

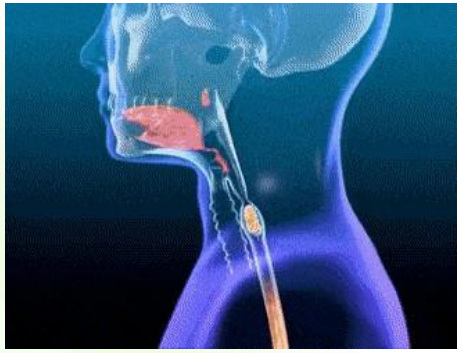
M Kemal Irmak[1*], Yesim Oztas[2] and Emin Oztas[3]

How?

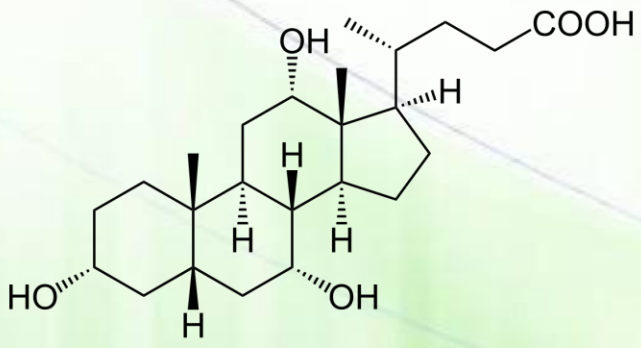


Stem cells
Immune factors
Nutrients
Non-coding RNA

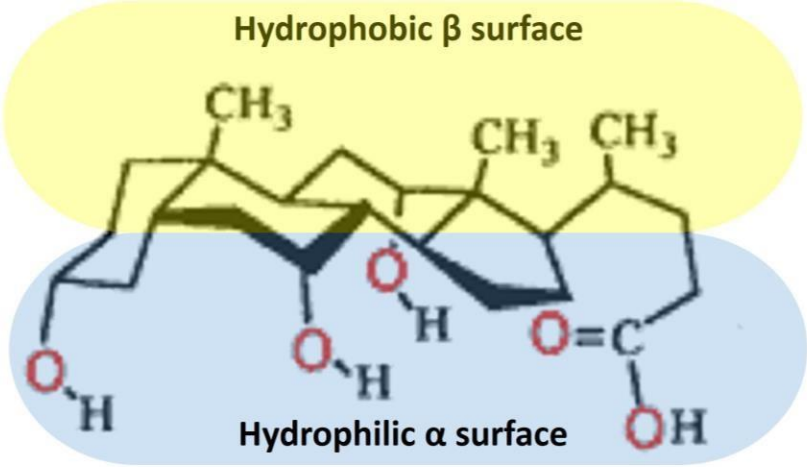
Emulsification: from drops to droplets

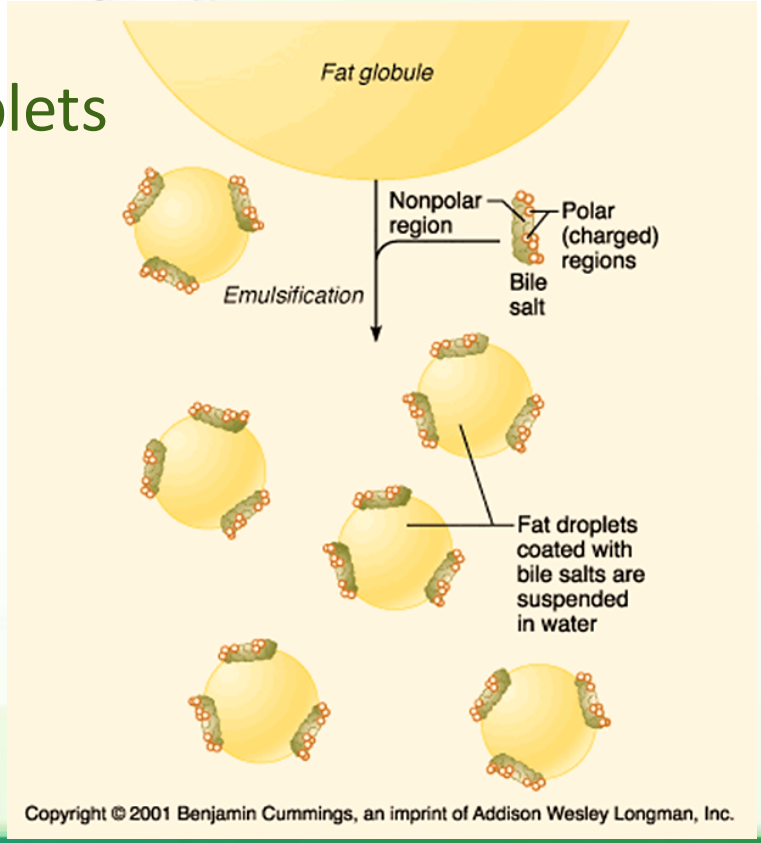


- Emulsification is defined as a process where one liquid is dispersed as small spherical droplets in a second immiscible (not homogeneous) liquid.
- Two mechanisms of emulsification in the duodenum:
  - Peristalsis: mechanical mixing leading to smaller droplets
  - Conjugated bile salts



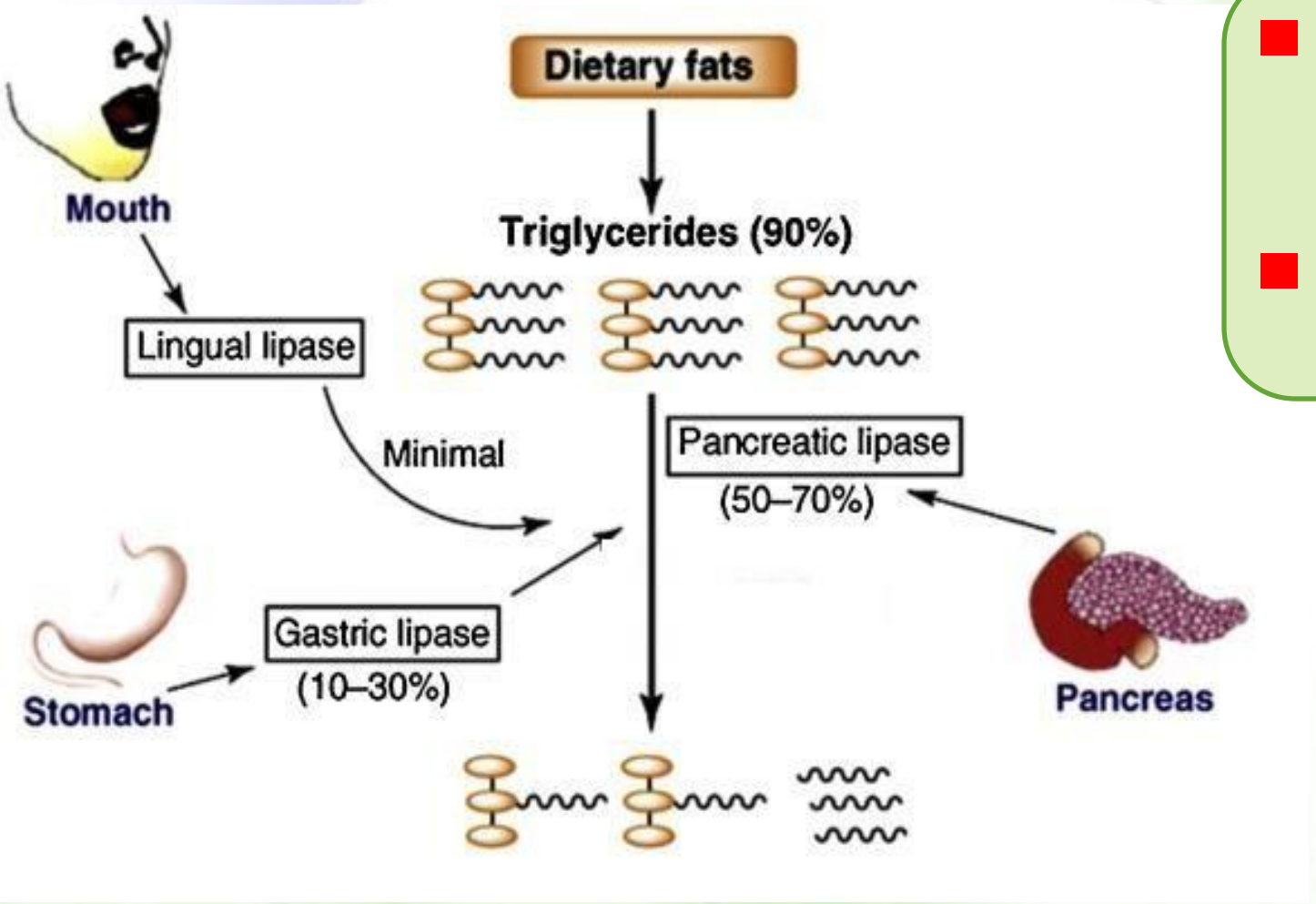
Cholic acid





- **The complement in this slide:** Because the environment in the intestine is aqueous, fats and lipids (Hydrophobic) reaching the small intestine need to be coated with molecules that make them dissolve in water in a process called emulsification. **It consists of two steps:**
- **the first step** is breaking them down mechanically into small droplets by smooth muscles of the oesophagus first (and they won't reattain their original form because the acidity of the stomach will prevent their renaturation) and then in the small intestine (peristalsis) so that they can be easily coated.
- **The second step** is conjugating them with bile salts, most important of which is cholic acid (derived from cholesterol). Bile salts are amphipathic in nature when you look at their 3D structure, so they have a hydrophobic surface that will interact with the fat droplets, and a hydrophilic surface that will make them soluble in water and this process facilitates absorption.

Degradation of triacylglycerol

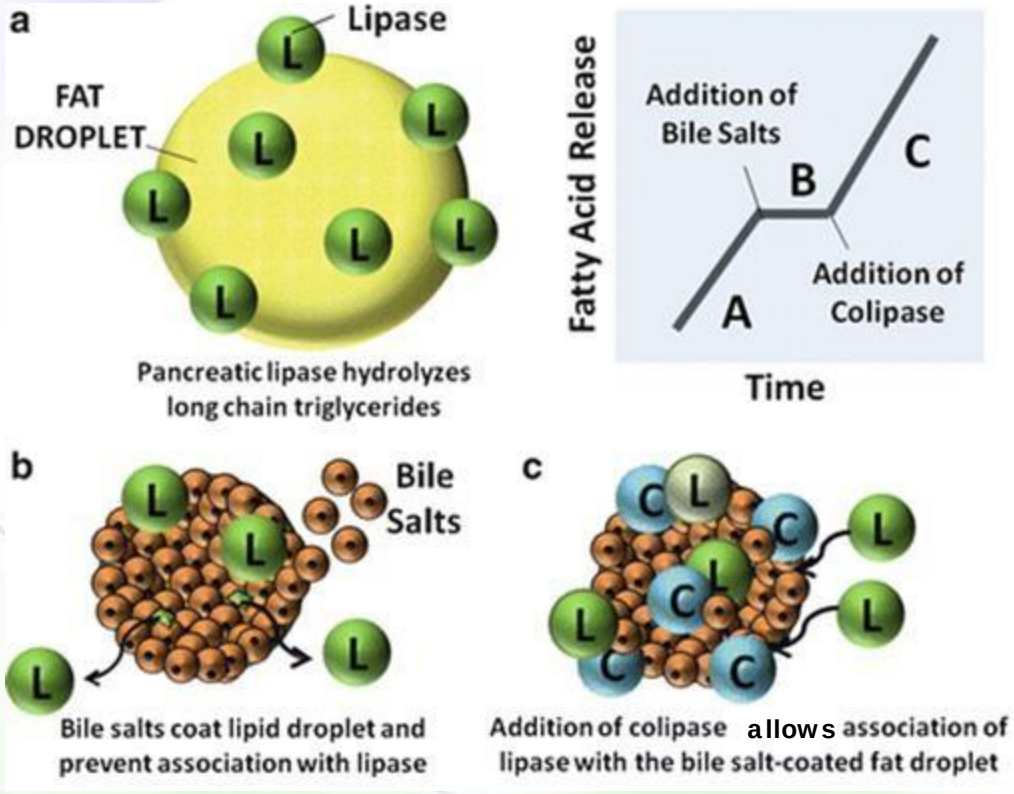


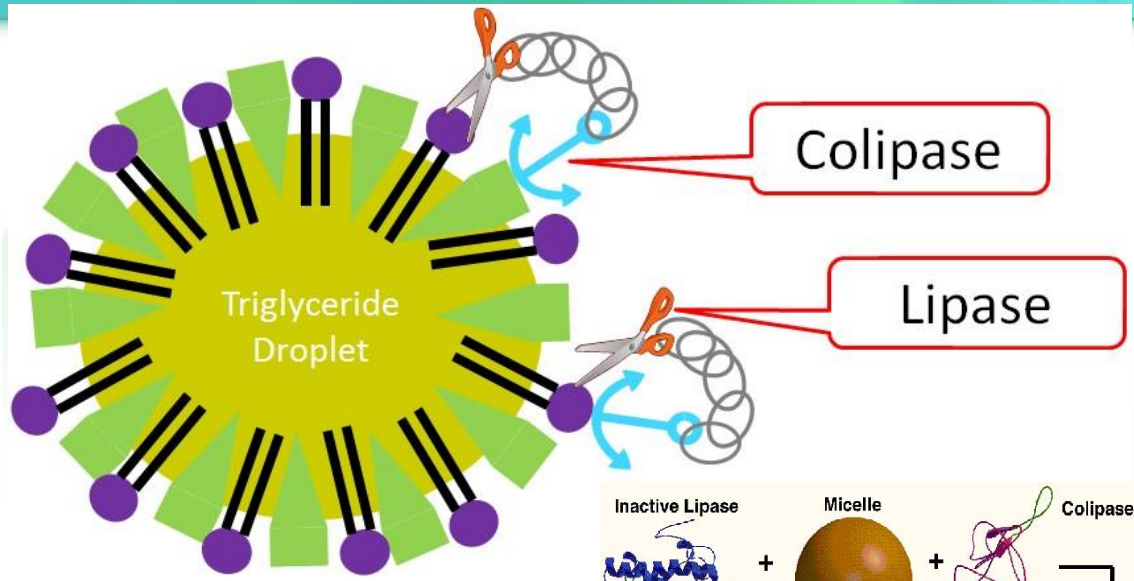
- **NOTE:** Lingual ligase -From the mouth- and gastric lipase from the stomach work together to get fatty acids from triacylglecrol. which is minimal.
- Gastric lipase is responsible for releasing up to 30% of FA fromTAG

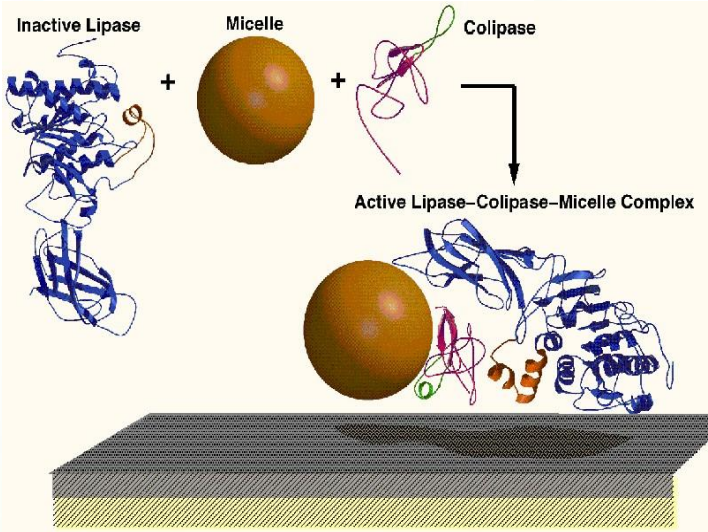
- **NOTE:** The majority of digestion occurs in the intestine by pancreatic lipase.

The significance of colipase

Pancreatic lipase is an interfacial enzyme that is most active at an oil-water interface







Combined pancreatic lipase-colipase deficiency is an orphan disease

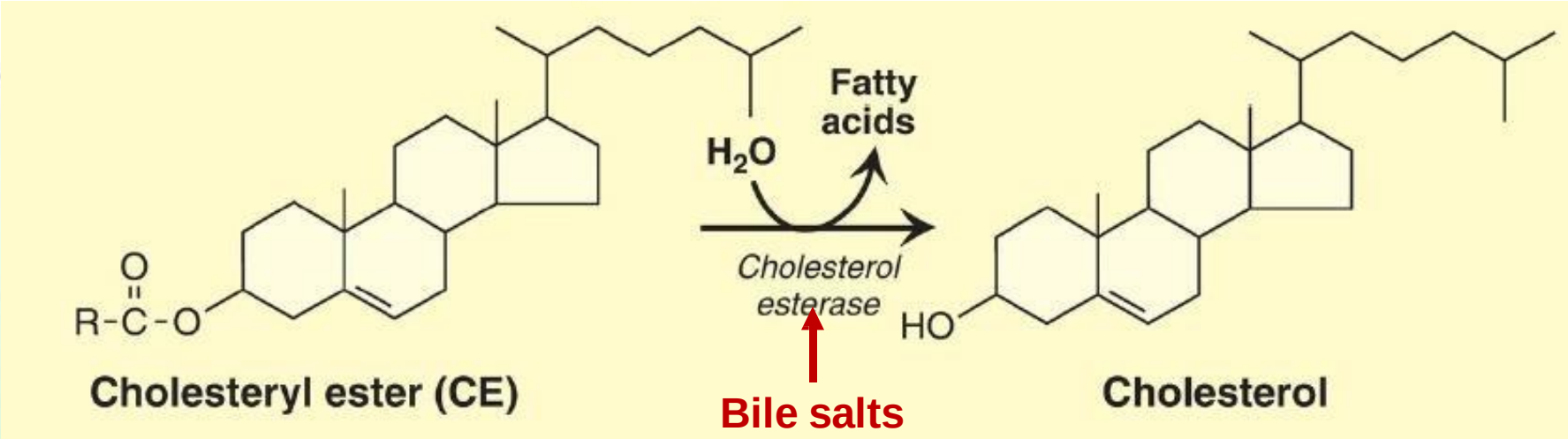
Colipase:

- Secreted as a zymogen(needs to be activated by proteolytic cleavage) from the pancreas
- Activated by trypsin
- Anchors lipase into the micelle interface at a ratio of 1:1
- Restores activity of lipase against inhibitors

- **The complement in this slide:** Pancreatic lipase can release FA from TAG in the absence of bile acid. However, in the presence of bile acid, Pancreatic lipase can't release fatty acids from TAGs because lipid molecules get encapsulated by bile salts (the phosphate groups prevent pancreatic lipase from releasing FA from TAG). The enzyme then can't function on its own. Pancreatic lipase needs protein called **Co-lipase** in order to carry out its function. Co-lipase binds lipase at ratio 1:1 (one co-lipase for one pancreatic lipase). Co-lipase helps lipase by binding at the surface of micelle, and making spaces between phosphate groups, so pancreatic lipase can carry out its function (releasing FA from TAG).

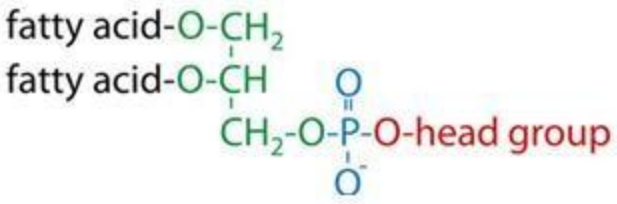
Degradation by cholesterol esters

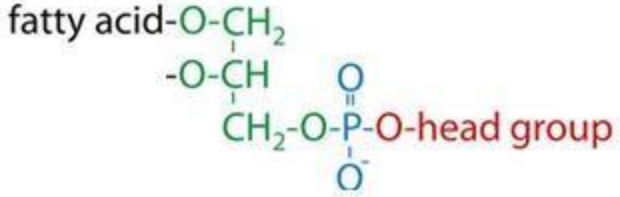
- **NOTE:** cholesterol esterase is the enzyme that responsible for releasing FA from cholesterol ester.
- Cholesterol esterase is activated by bile salts.
- Cholesterol ester: cholesterol with fatty acids.
- Most of the cholesterol is free in intestines.

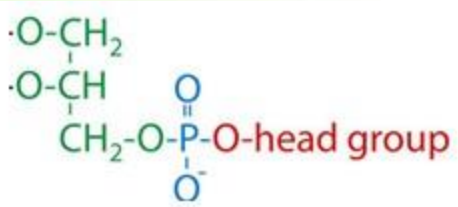


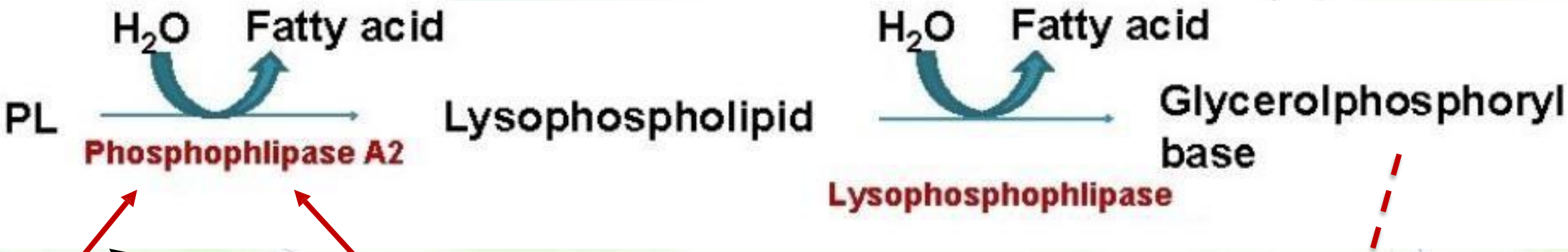
85-90%

Degradation of phospholipids









Pro-PLA2

Trypsin

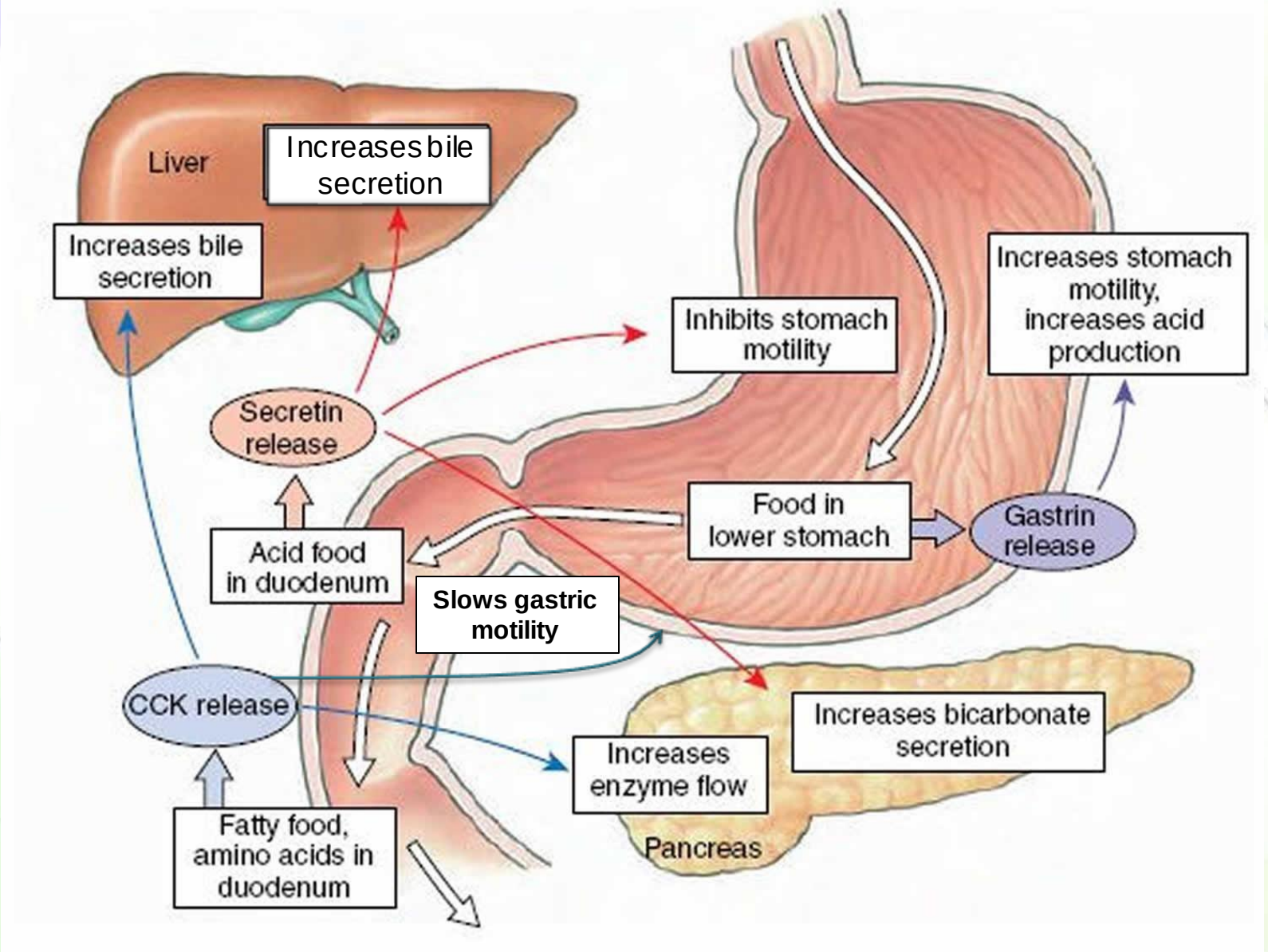
Bile salts

- *Excreted in the feces*
- *Further degraded*
- *Absorbed*

- **The complement in this slide: Phospholipase A2 is secreted as zymogen "Pro-PLA2". It is activated by trypsin and bile salts.**
- **1. PLA2 releases one FA from carbon no.2 to give lysophospholipid.**
- **2. Lysophospholipase releases one FA from carbon no. 1 to give glycerolphosphoryl base (glycerol with only one phosphate).**

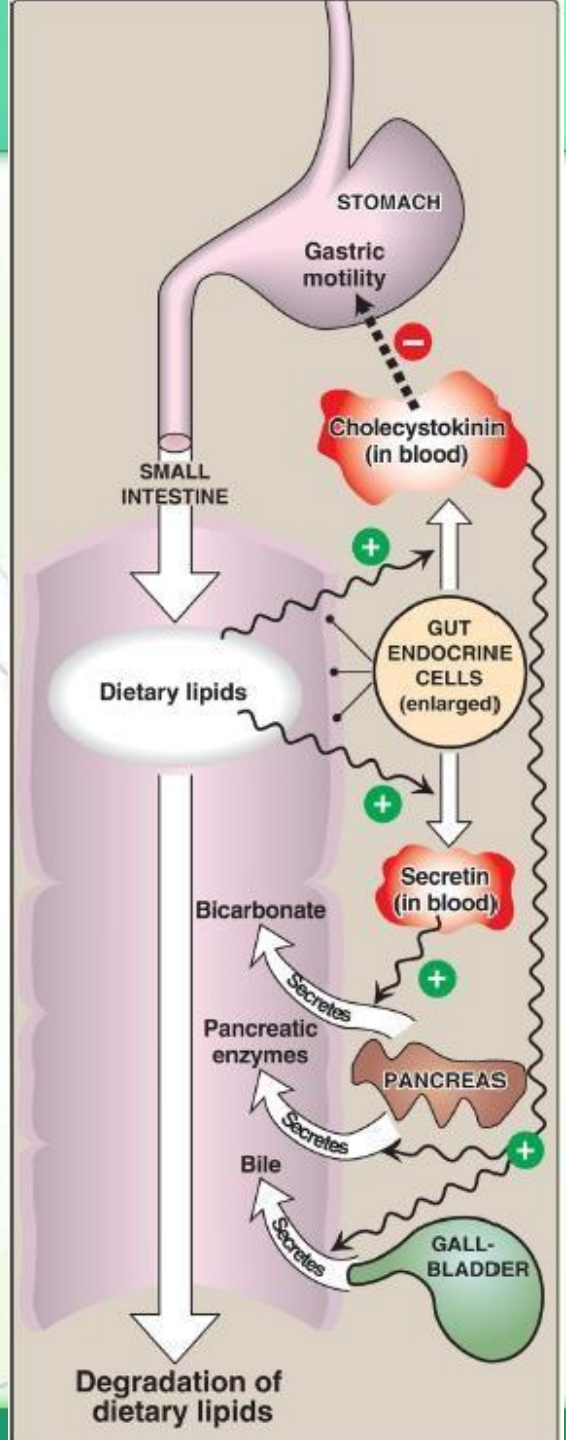
- **SO by those mechanisms, we simplify lipid molecules in side the intestine.**

Hormonal control



Hormonal control

- Entry of food (chyme) induces the release cholecystokinin (CCK; a peptide hormone) from the duodenum and jejunum.
  - Induces contraction of the gallbladder to release bile (bile salts, phospholipids, and free cholesterol)
  - Acts on the exocrine pancreatic cells to release digestive enzymes
  - Decreases gastric motility to slow down the release of gastric contents
- The low pH of the chyme entering the intestine induces intestinal cells to produce secretin (a peptide hormone).
  - Causes the pancreas to release a bicarbonate-rich solution to neutralize the pH and make it optimal for the digestive pancreatic enzymes.
  - Inhibits gastric motility.



- **The complement in this slide:** When chyme (food) reaches the stomach, it stimulates it to release gastrin which increases the stomach motility, acid and trypsin secretion.

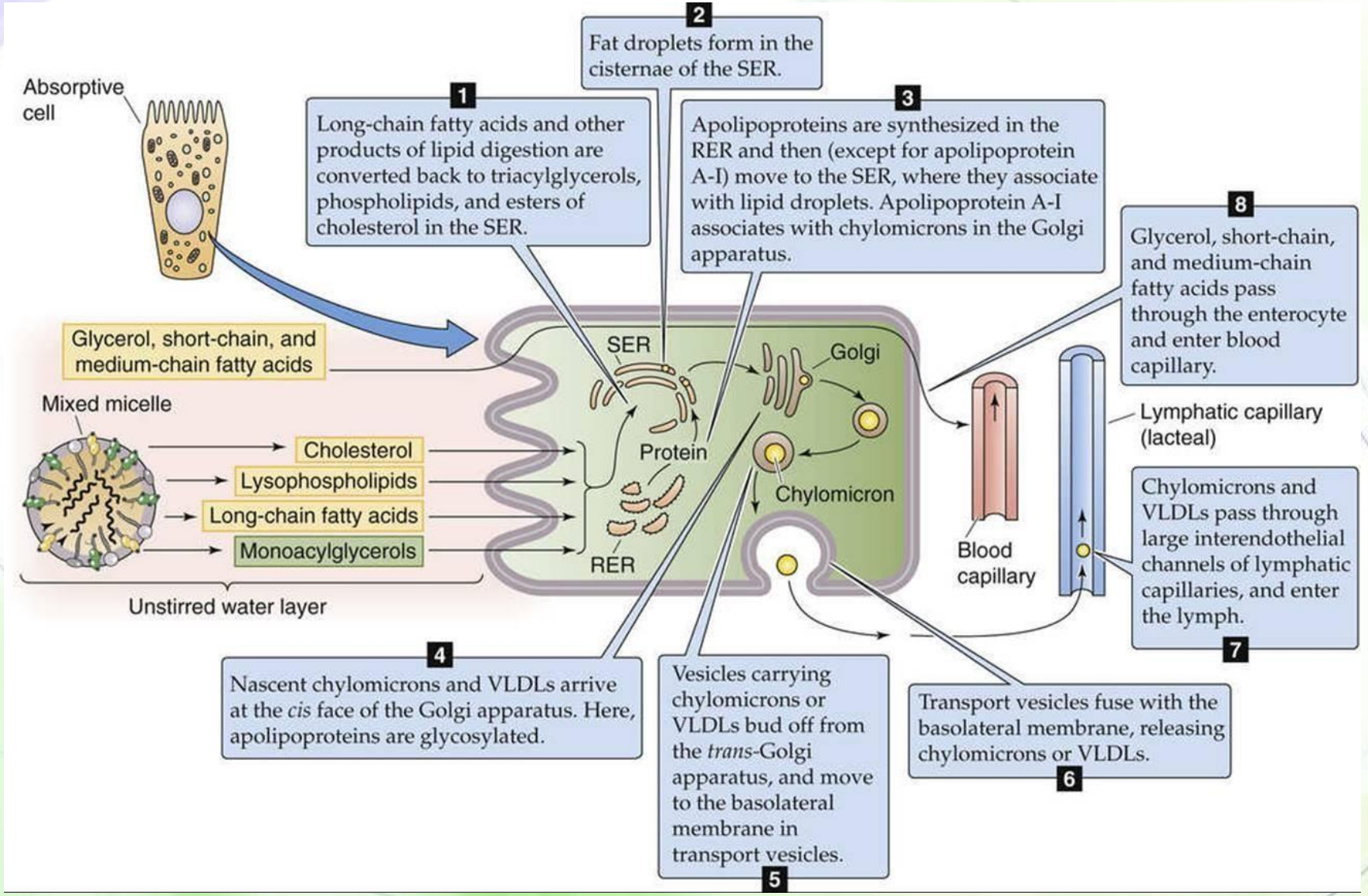
When it reaches intestine, it stimulates releasing of two hormones:

- 1. CCK
  - Stomach: motility ↓
  - Liver: bile salts ↑
  - Pancreas: digestive enzyme flow ↑

- 2. Followed by Secretin
  - Stomach: motility ↓
  - Liver: bile salts ↑
  - Pancreas: bicarbonate ↑

❖ Bicarbonate: neutralisation of acidic juice that comes from the stomach and activates other enzyme.

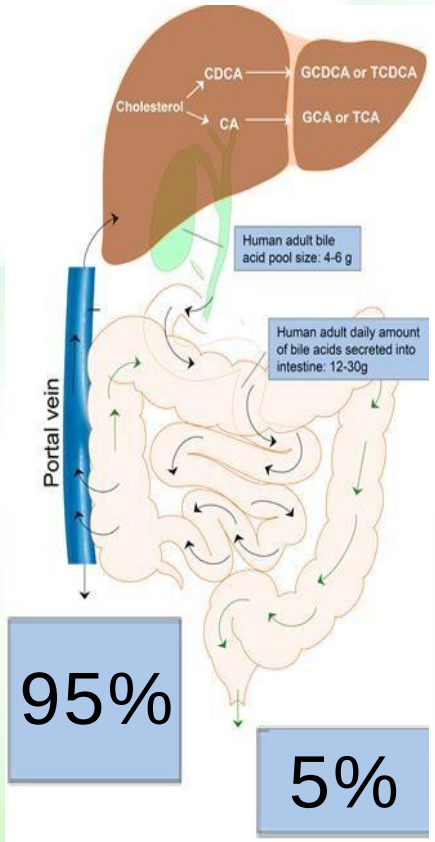
❖ As the optimal Ph of digestive enzymes is about 8, bicarbonate increases the Ph in order to activate them.

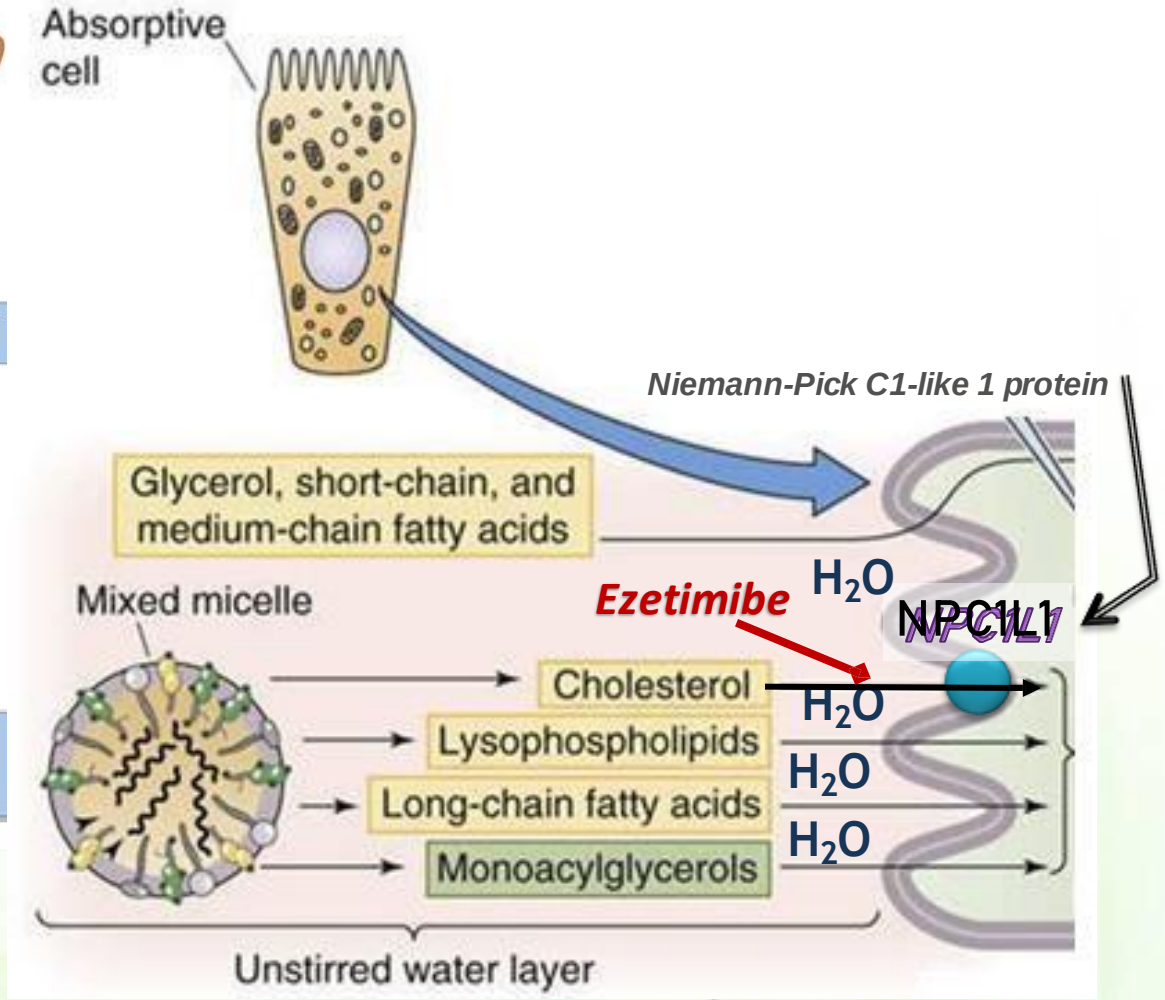

Absorptive cell
1
Long-chain fatty acids and other products of lipid digestion are converted back to triacylglycerols, phospholipids, and esters of cholesterol in the SER.
2
Fat droplets form in the cisternae of the SER.
3
Apolipoproteins are synthesized in the RER and then (except for apolipoprotein A-I) move to the SER, where they associate with lipid droplets. Apolipoprotein A-I associates with chylomicrons in the Golgi apparatus.
8
Glycerol, short-chain, and medium-chain fatty acids pass through the enterocyte and enter blood capillary.
Glycerol, short-chain, and medium-chain fatty acids
Mixed micelle
Cholesterol
Lysophospholipids
Long-chain fatty acids
Monoacylglycerols
Unstirred water layer
SER
Golgi
Protein
Chylomicron
RER
Blood capillary
Lymphatic capillary (lacteal)
Chylomicrons and VLDLs pass through large interendothelial channels of lymphatic capillaries, and enter the lymph.
7
4
Nascent chylomicrons and VLDLs arrive at the *cis* face of the Golgi apparatus. Here, apolipoproteins are glycosylated.
5
Vesicles carrying chylomicrons or VLDLs bud off from the *trans*-Golgi apparatus, and move to the basolateral membrane in transport vesicles.
6
Transport vesicles fuse with the basolateral membrane, releasing chylomicrons or VLDLs.

Absorption by enterocytes

- Mixed micelles are formed in the lumen from free fatty acids (FFA), monoacylglycerol, free cholesterol, bile salts, and fat-soluble vitamins.
- Cholesterol is poorly absorbed.
  - Note: it can be drug-targeted
- The uptake of fatty acids across the enterocyte brush- border membrane occurs by passive diffusion and by protein–mediated mechanisms.

  Short- and medium-chain FAs are directly absorbed by passive
- diffusion to the blood (Apical surface of enterocytes —> basolateral suture —> blood stream .



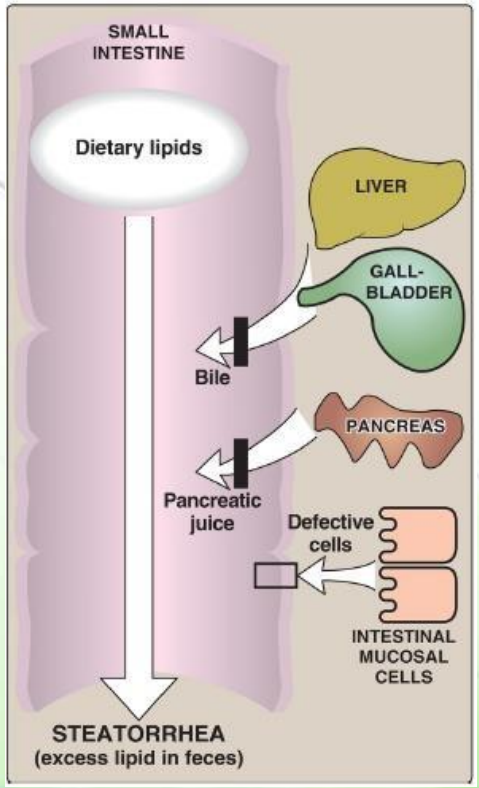


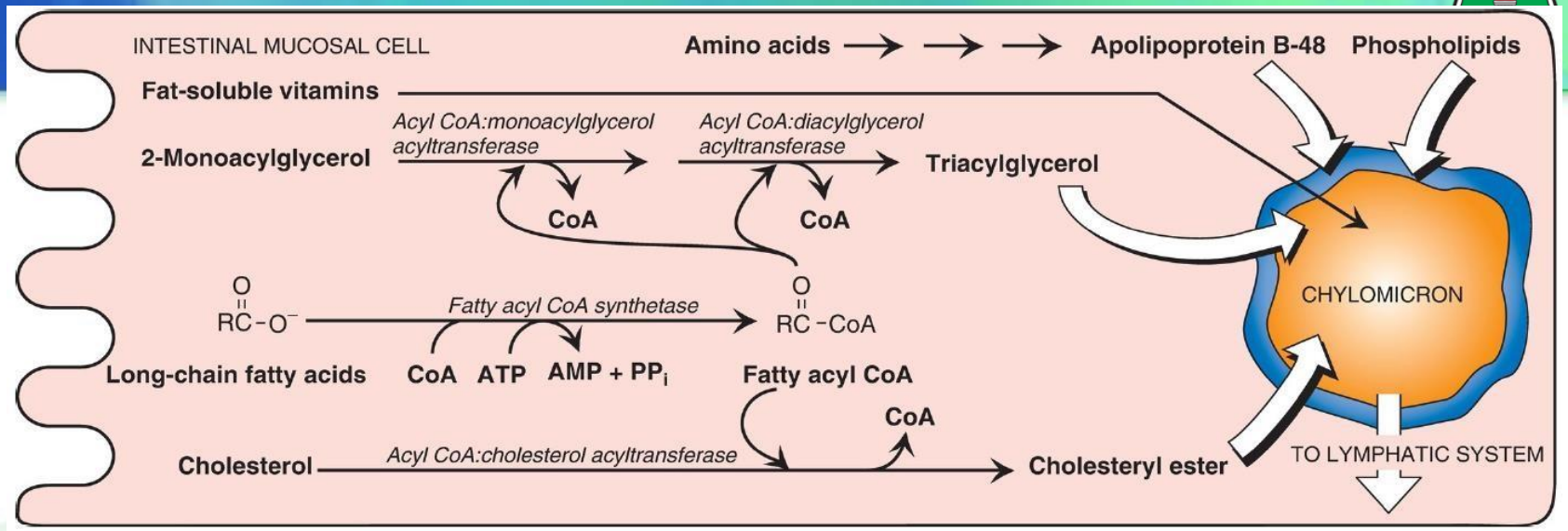
- **The complement in this slide:** NPC1L1 (Nlemman-Pick C1-like 1 protein ‘it’s a carrier’) can be drug targeted by ezetimibe, which lowers the absorption of cholesterol.
- People with high cholesterol level are given statin, which decreases the blood cholesterol level by inhibits synthesis of it.

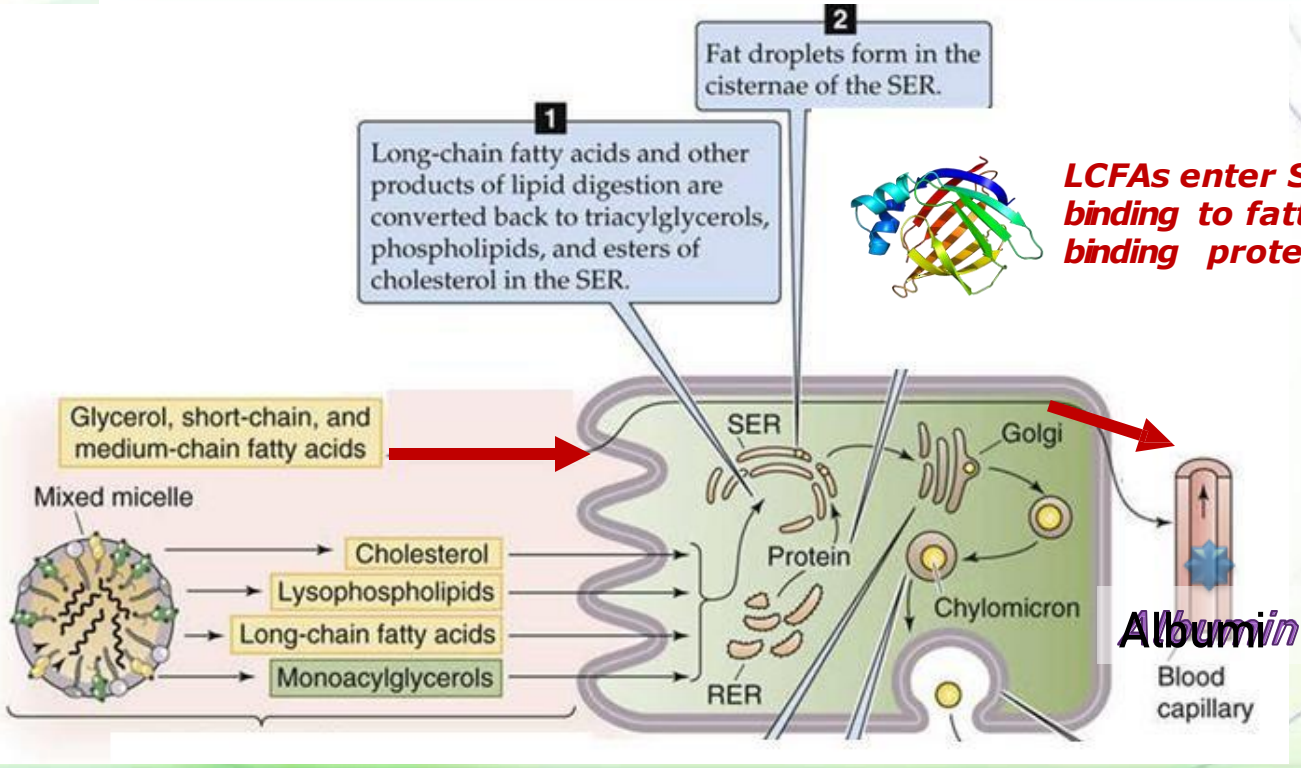
Reformation of complex lipids

Principal causes of steatorrhea:

1. ***Short bowel disease***
2. ***Liver or biliary tract disease***
3. ***Pancreatic exocrine insufficiency***
4. ***Cystic fibrosis***





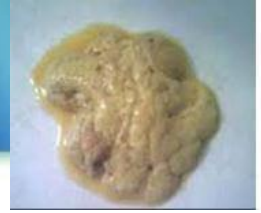


LCFAs enter SER by binding to fatty acid–binding protein 2 (FABP2)

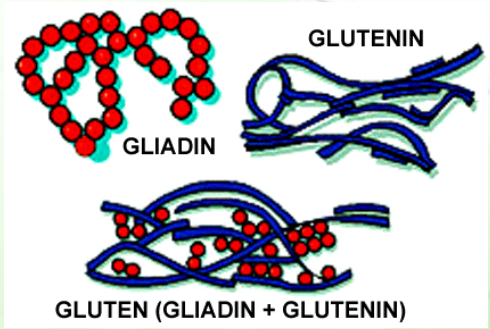
Albumin

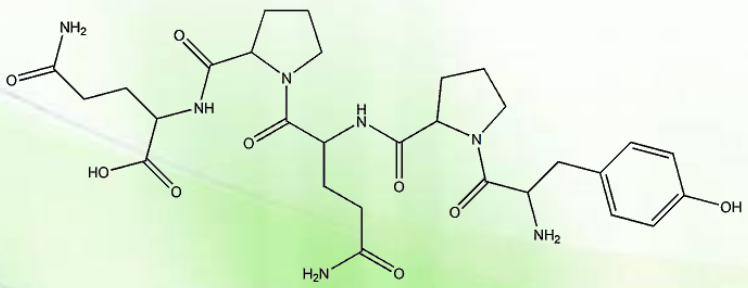
- **The complement in this slide:**
- LCFAs enter SER by binding to fatty acid–binding protein 2 (FABP2), LCFAs can :
  - Forming TAG by FA esterification with glycerol.
  - Forming phospholipids.
  - Forming cholesterol esters (FA + cholesterol).
- All the above in addition to lipid soluble vitamins are packed in chylomicrons.

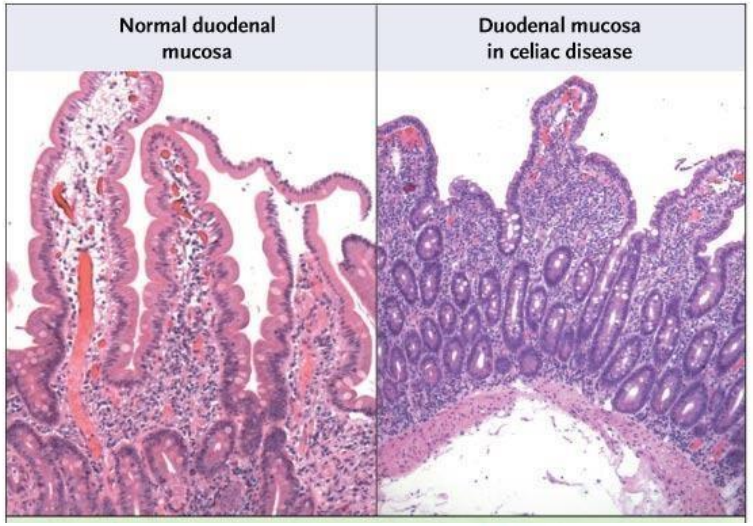
Celiac disease (CD)

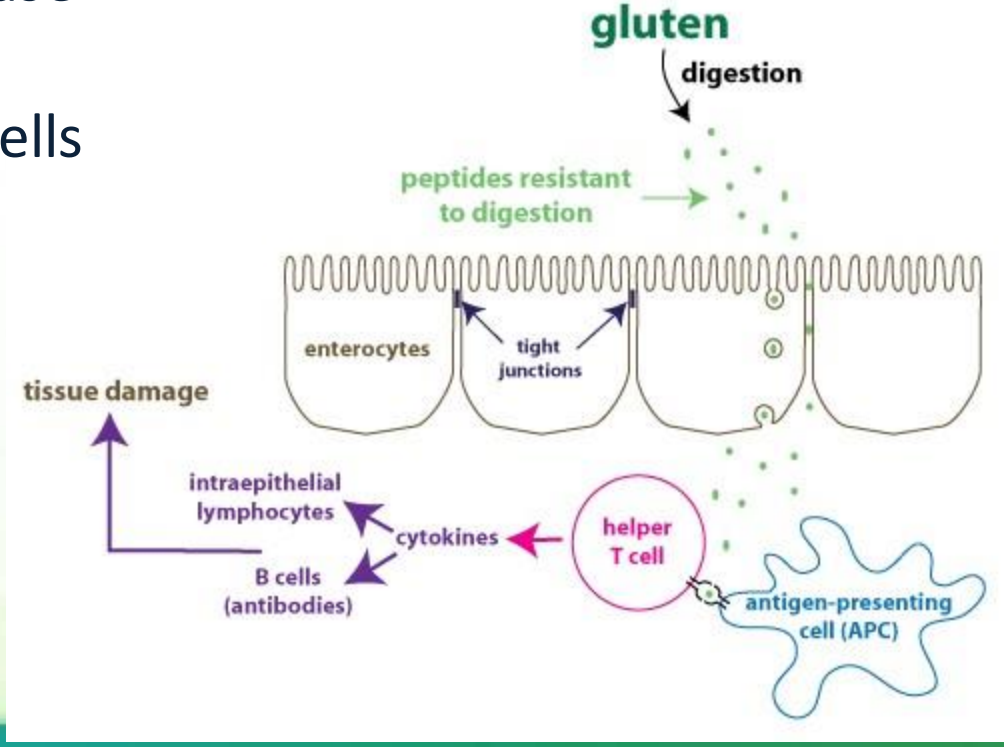


- Fat malabsorption leading to steatorrhea
- It is an autoimmune response to gliadin, a peptide found in gluten (wheat, rye, and barley).
- Gliadin contains many proline (14%) and glutamine (40%) residues, making it resistant to digestion.
- Lab tests: the presence of anti-tissue transglutaminase (anti-tTG) antibodies.
- Tissue biopsy: absence of villous surface epithelial cells resulting in decreased nutrient absorption.







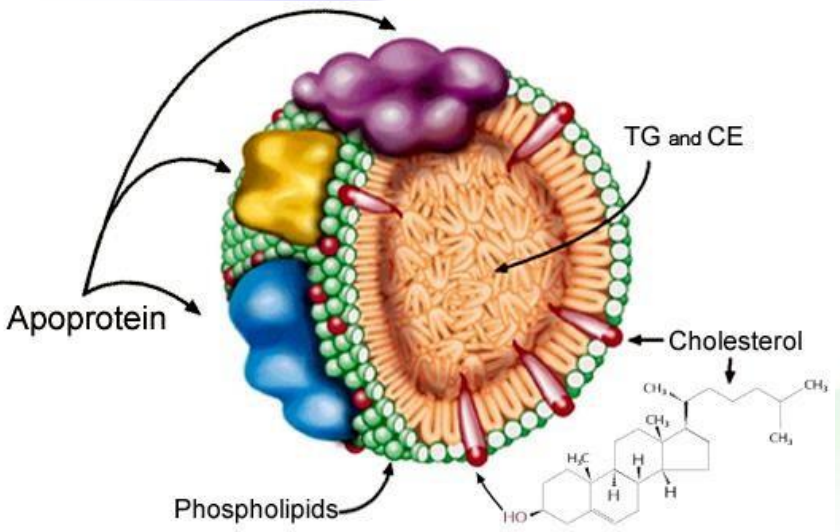


http://courses.washington.edu/pbio376/celiac/celiacdisease-376.html

- **The complement in this slide:** there are diseases associated with malabsorption of lipid, including:
  - Short bowl syndrome (in case of cutting part of the intestine due to cancer).
  - Deficiency in production of pancreatic digestive enzymes .
  - Problem in production of bile acid.
  - Cystic fibrosis (due to defect CFTR protein that balance the Cl and Na ions and water levels). In cystic fibrosis, the mucus becomes more viscous, so the absorption becomes difficult. Patients with cystic fibrosis also become exposed to recurrent infections (as we said in immunology).

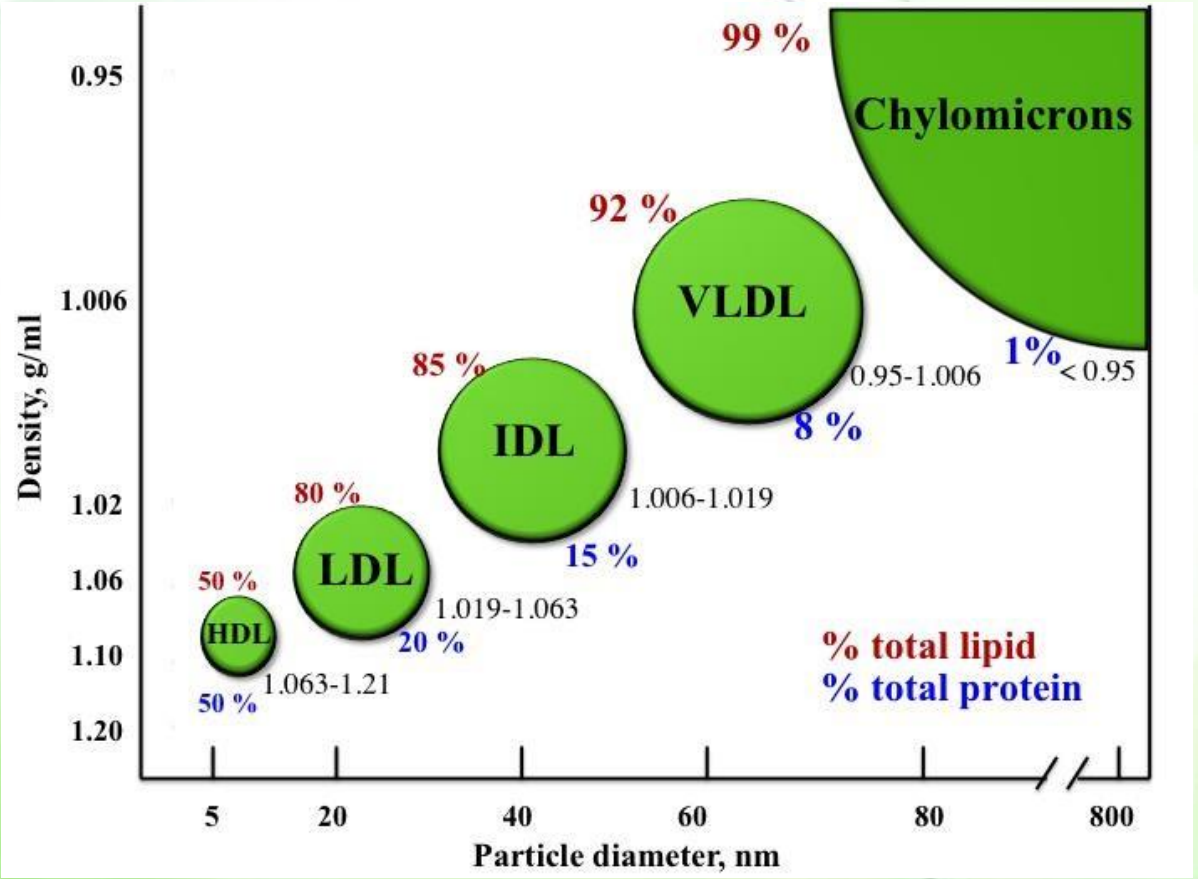
- **The complement in this slide:** Celiac disease is an autoimmune response to **gliadin**
Gluten is a protein composed of 2 poly peptide chains, **glutenin** and **gliadin**.
Gliadin is rich in proline and glutamine, making it resistant to digestion, resulting in inflammatory response(this inflammatory response damages the enterocytes).
Scientists found that patients with celiac disease have antibodies against enzyme known as **transglutaminase**. Celiac disease is an autoimmune disease.

Lipoproteins



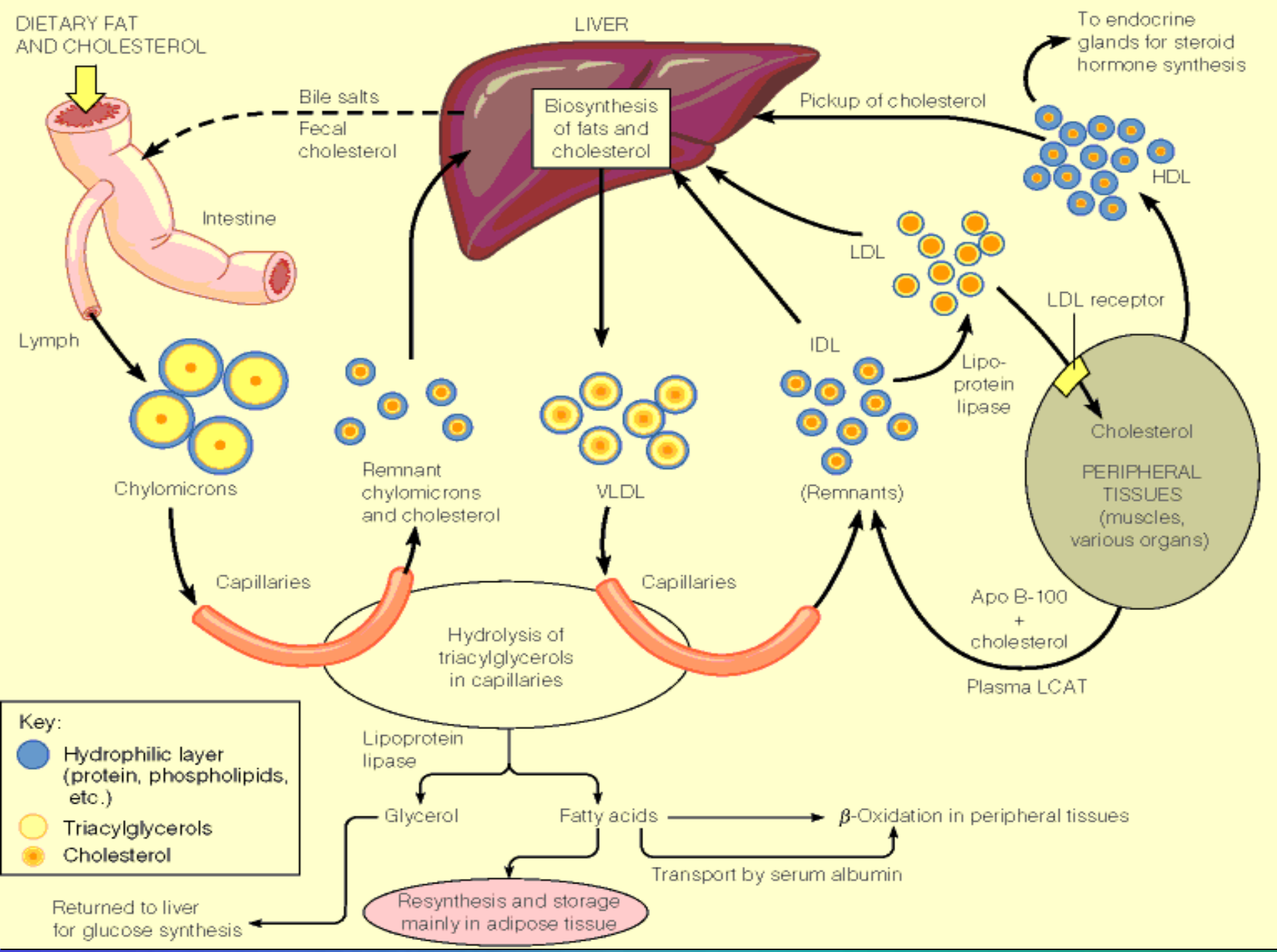
Function: transport of lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) in blood plasma.

As lipid content increases, the density decreases



Composition of lipoproteins

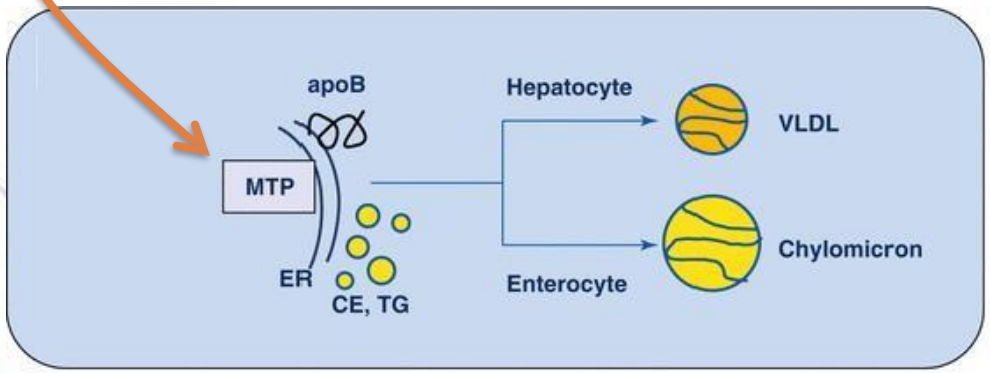
	Chylomicrons	VLDL	LDL	HDL
Density (g/ml)	< 0.94	0.94-1.006	1.006-1.063	1.063-1.210
Diameter (Å)	2000-6000	600	250	70-120
Site of synthesis	Intestine	Liver	Liver	Liver, intestine
Total lipid (wt%)	99	92	85	50
Triacylglycerols	85	55 Liver	10	6
Cholesterol esters	3	18	50 (bad)	40 (good)
Apolipoproteins	A, C, E, **B48**	C, **B100**, E	B100	A, C, E
Function	Transport of dietary TG to the liver	Transport of TG from the liver to peripheral tissues	Transport of cholesterol from the liver to peripheral tissues	Transport of cholesterol from peripheral tissues back to the liver (cholesterol scavengers)

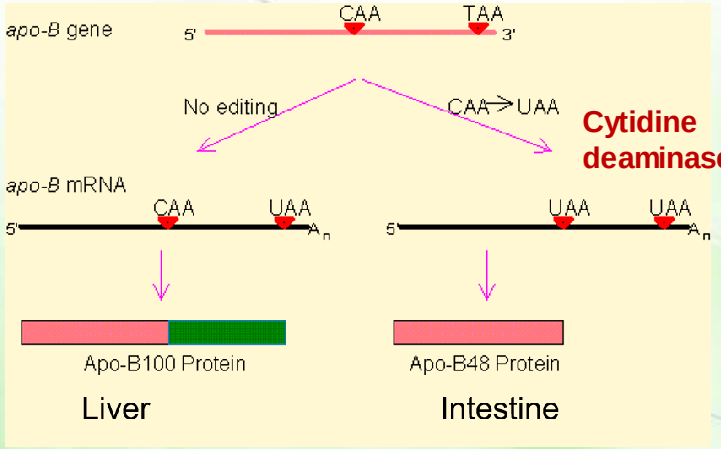


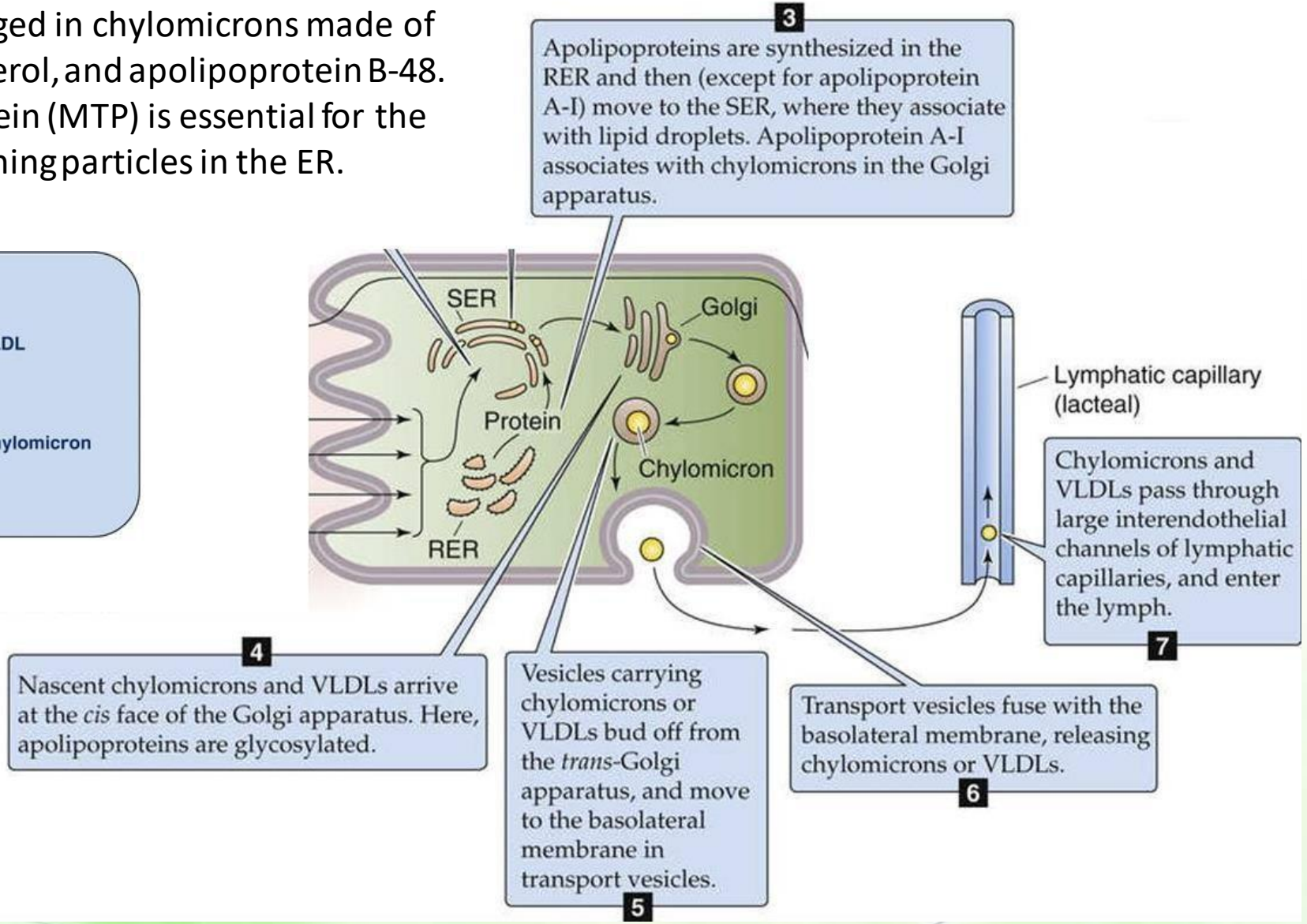
Lipid transport

Formation and release of chylomicrons

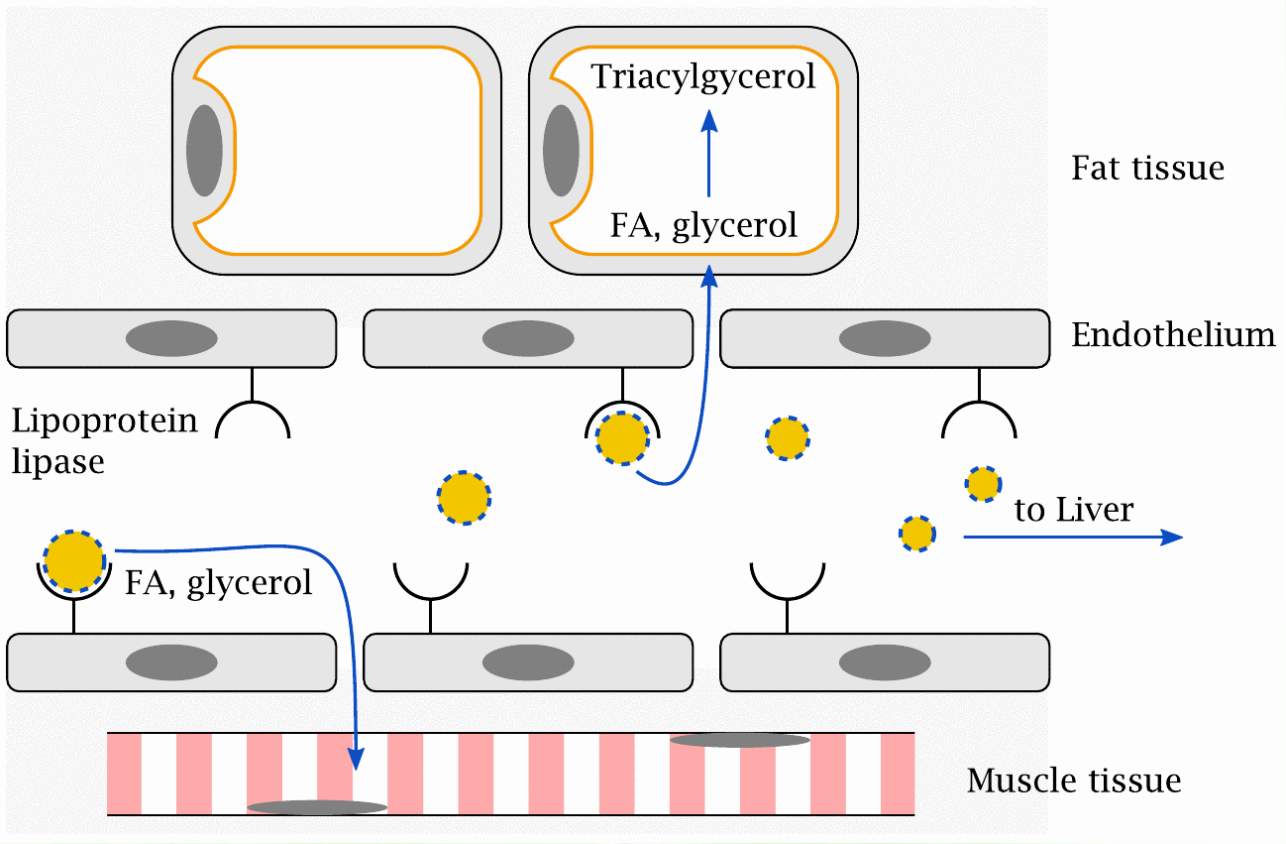
- TAG and cholesteryl esters are packaged in chylomicrons made of phospholipids, nonesterified cholesterol, and apolipoprotein B-48.
- Microsomal triglyceride transfer protein (MTP) is essential for the assembly of all TAG-rich apoB-containing particles in the ER.







Fates of TAGs in chylomicrons



- TAGs in chylomicrons are hydrolyzed in the bloodstream by lipoprotein lipases that are anchored into the surface of endothelial cells.

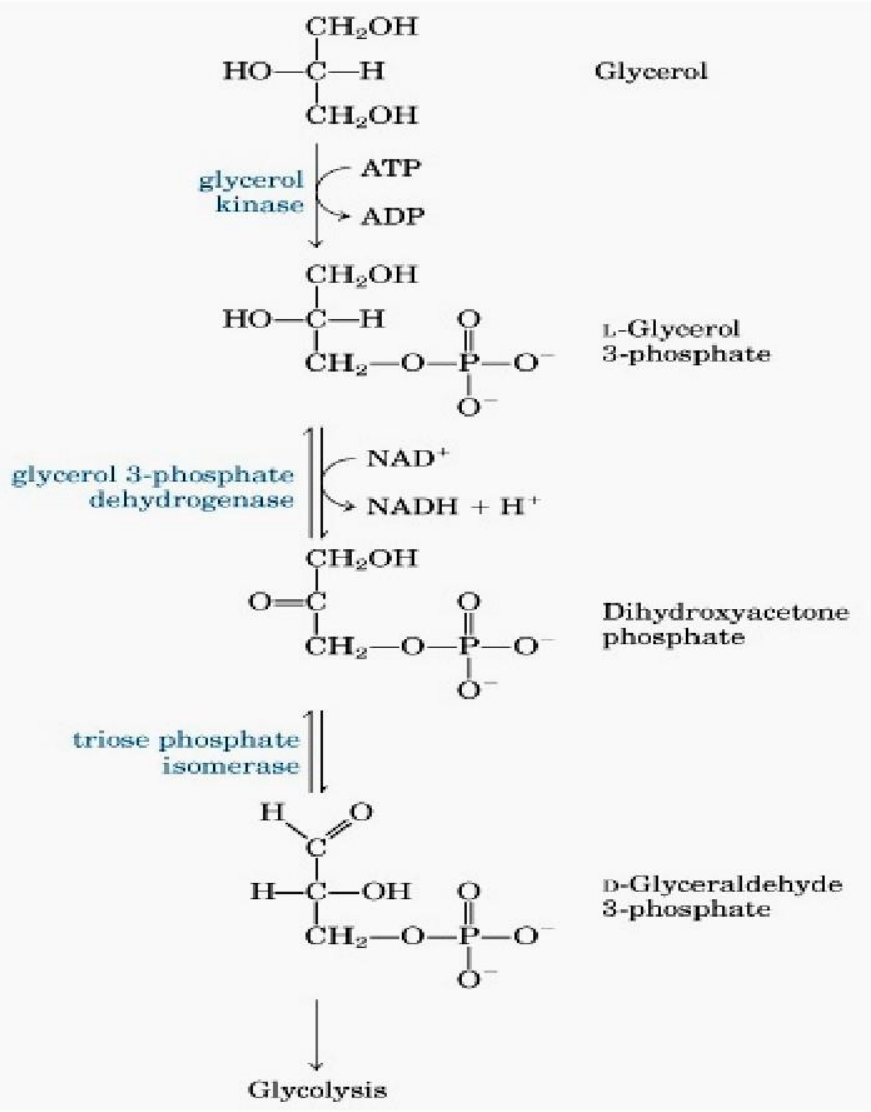
- The resulting fatty acids have two possible fates:

(1) When energy is in good supply, they are converted back to TAGs for storage in adipose tissues.

(2) When cells need energy, the fatty acids are oxidized into acetyl-CoA.

Familial chylomicronemia (type I hyperlipoproteinemia) is a rare, autosomal-recessive disorder caused by a deficiency of LPL or its coenzyme apo C-II resulting in fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis.

Fate of glycerol



- Glycerol is carried in the bloodstream to the liver or kidneys, where it is phosphorylated and then converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) for either glycolysis or gluconeogenesis or synthesis of TAG.

اللهم انصر أهل غزة وثبت أقدامهم
اللهم احرس أهل غزة بعينك التي لا تنام
اللهُم كُن لأهل غزة عونًا ونصيرًا
اللهم إنا لا نملك لفلسطين إلا الدعاء فيارب لا ترد
لنا دعاء ولا تخيب لنا رجاء وأنت أرحم الراحمين

V2: SLIDE 25

PRO-PLA2 INSTEAD OF PRO-PLA1