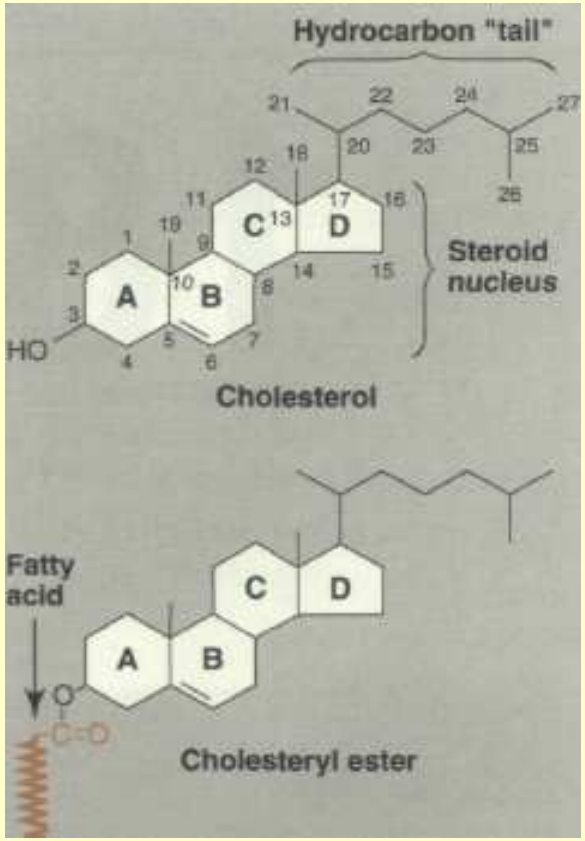
Cholesterol metabolism

- Function
- Biosynthesis
- Transport in the organism
- Hypercholesterolemia

Cholesterol

- component of all cell membranes
- precursor of bile acids
  steroid hormones
  vitamin D



Sources: dietary cholesterol (~ 25% of a daily turnover) - 0,3g/day

synthesis in tissues (~ 75 %) - 1 g/day

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liver

(reproductive tissues -adrenal cortex, ovaries, testes, placenta)

enzymes of biosynthesis present in virtually all tissues

Transport:

as a component of lipoproteins, most as cholesteryl esters

chylomicrons: intestine → liver

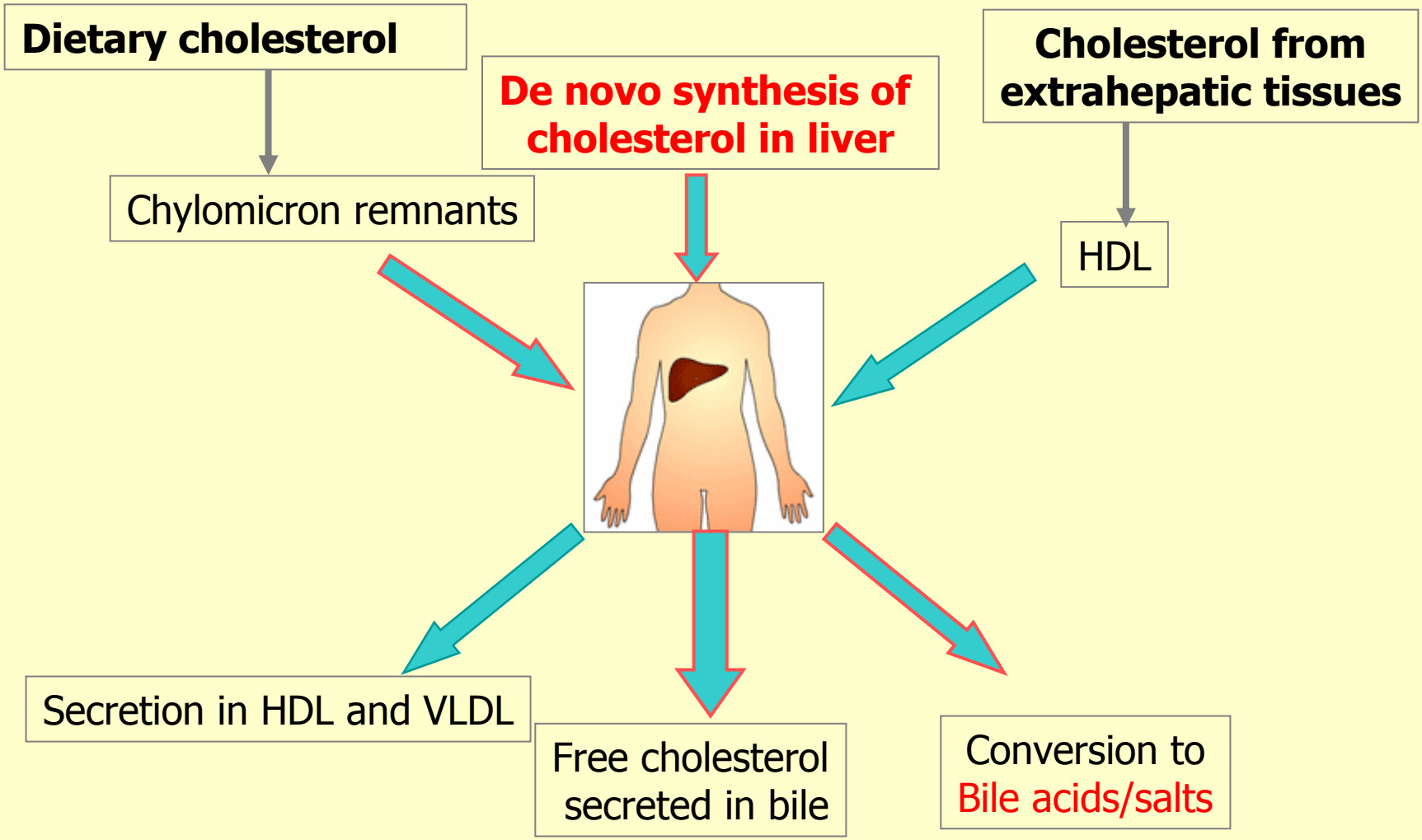
VLDL: liver → plasma

LDL: plasma → extrahepatic tissues

HDL: plasma → liver

(extrahepatic tissues) → plasma

Overview of cholesterol metabolism in liver



Cholesterol excretion

! ***Steroid ring can not be cleaved in humans***

1. cholesterol $\xrightarrow{\text{liver}}$ bile acids/salts $\longrightarrow$ bile $\longrightarrow$ intestine $\longrightarrow$ feces

2. cholesterol $\longrightarrow$ bile $\longrightarrow$ intestine $\longrightarrow$ cholestanol / koprostanol $\longrightarrow$ feces

Cholesterol availability in diets widely varies ⇒ regulatory mechanisms

balance the rate: **cholesterol synthesis** $\longleftrightarrow$ **cholesterol excretion**

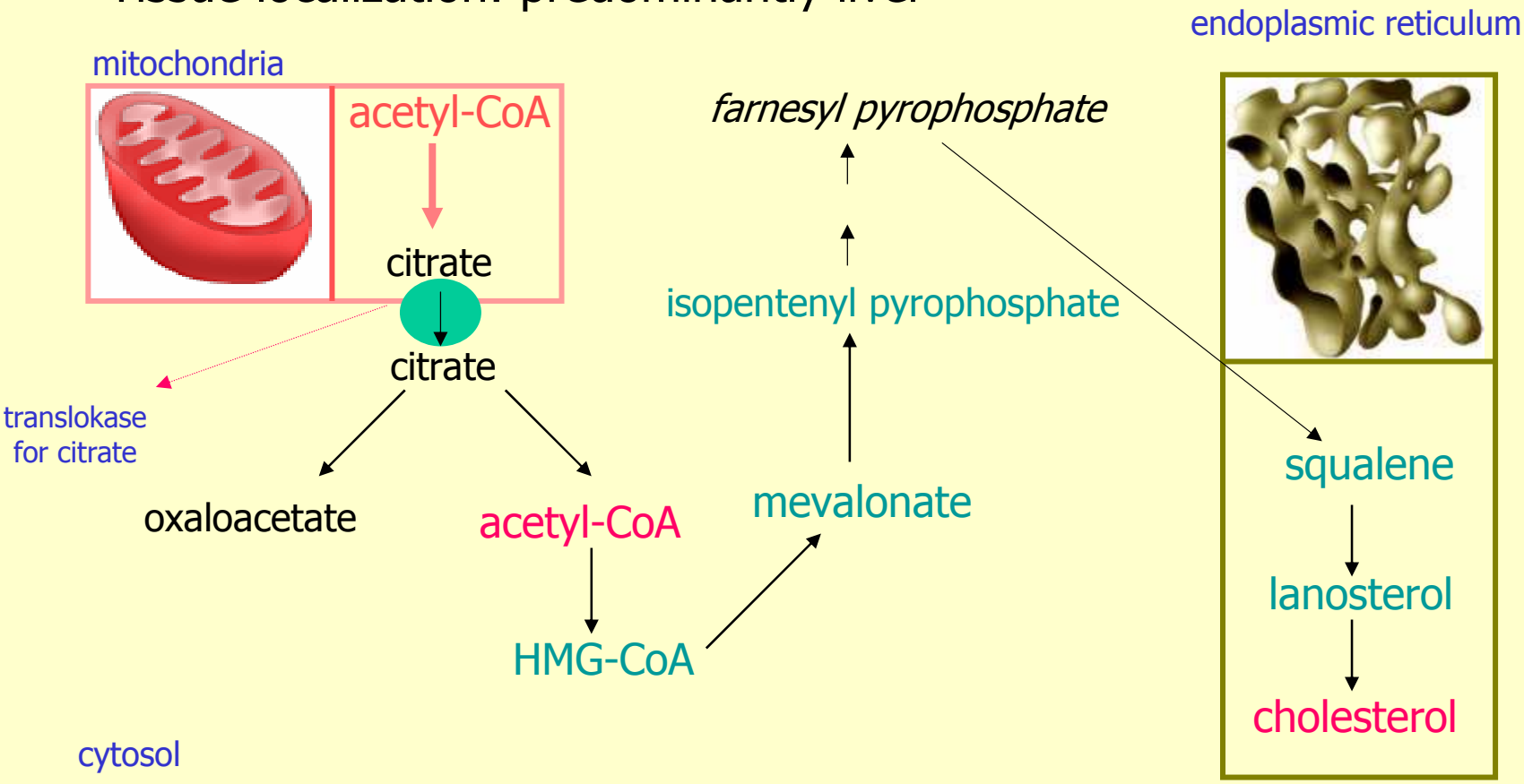
Imbalance:

elevation of circulating cholesterol $\longrightarrow$ **coronary artery disease**

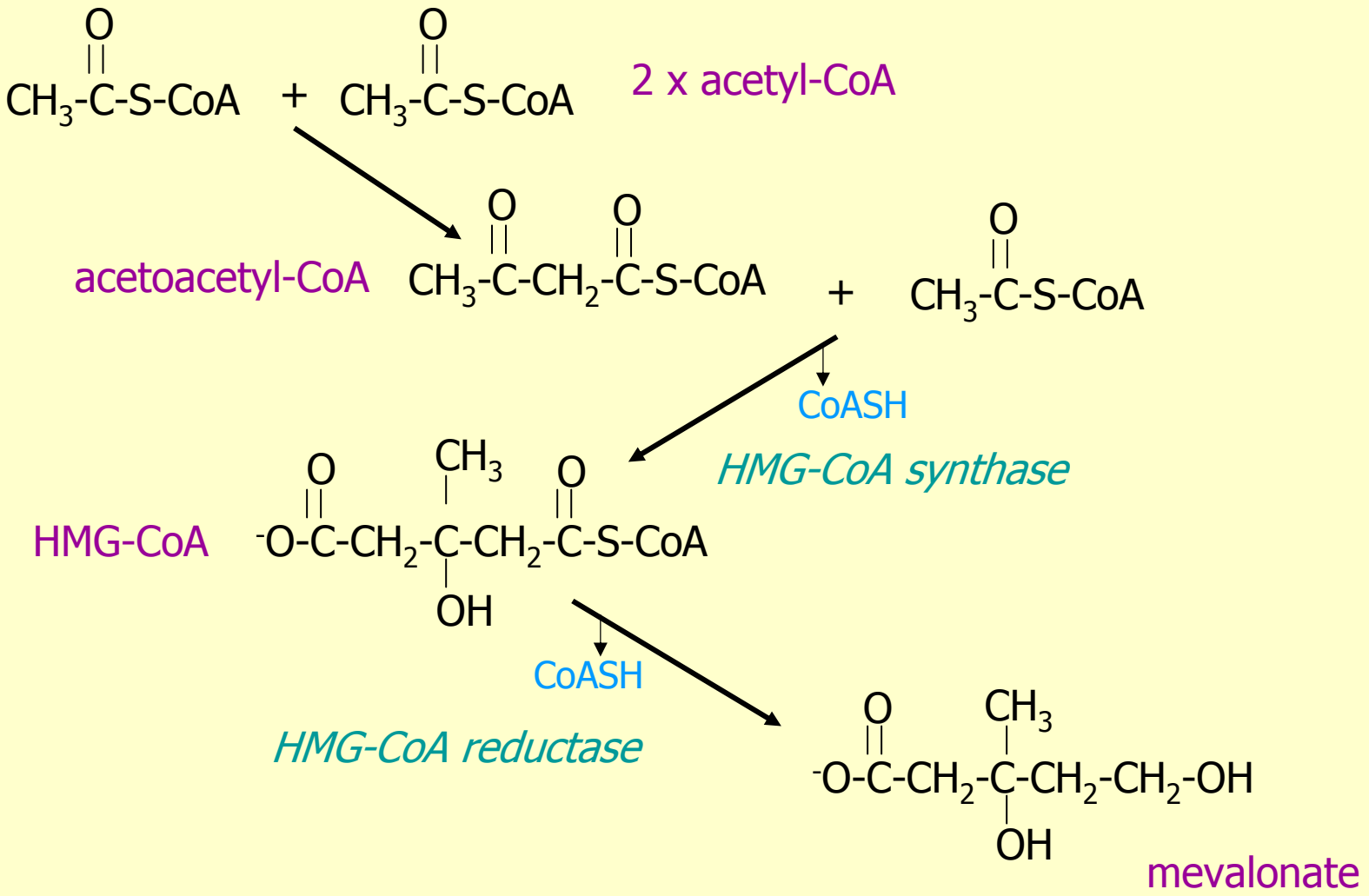
excessive cholesterol excretion into bile $\longrightarrow$ precipitation in the gallblader and bile duct $\longrightarrow$ **gallstones**

Cholesterol biosynthesis

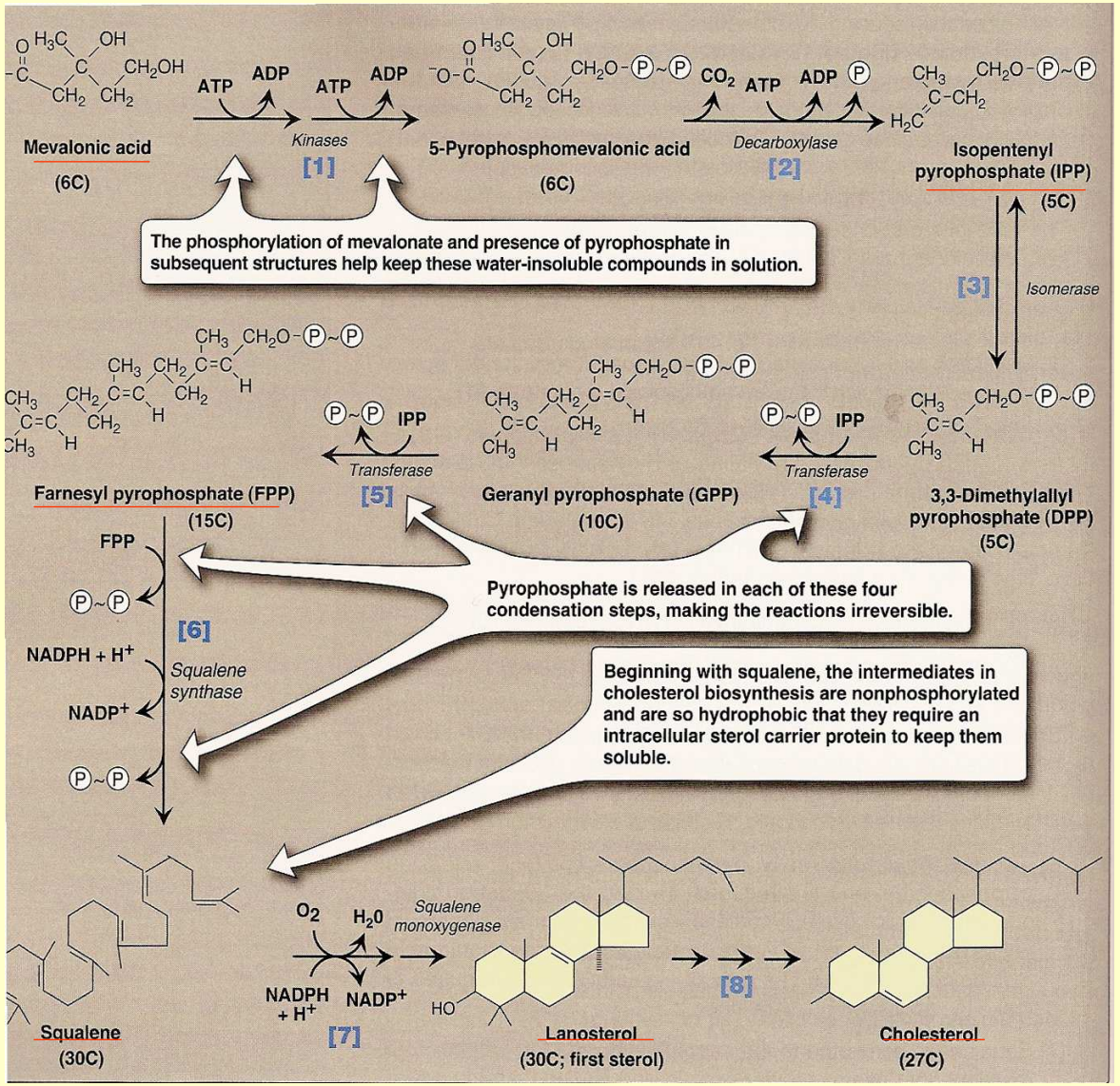
Initial substrate: acetyl-CoA
Tissue localization: predominantly liver



Cholesterol biosynthesis: acetyl-CoA ⟶ mevalonate

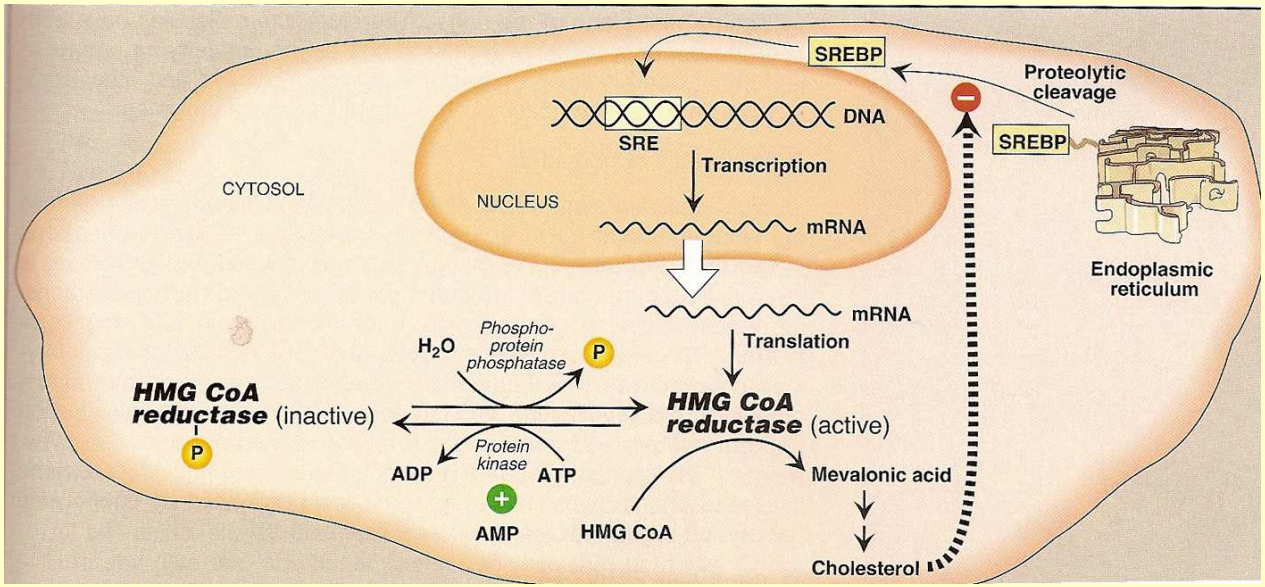


Cholesterol biosynthesis: mevalonate ⟶ cholesterol



Control of cholesterol synthesis

Regulation of HMG CoA reductase, rate-limiting enzyme of cholesterol synthesis



SRE = sterol regulatory element

SREBP = sterol regulatory binding protein – transcription factor associated with ER membrane

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proteolytic release

↓

binding to DNA at SRE

↓

transcription of HMG CoA reductase

blocked by cholesterol

1. Regulation of transcription (HMG CoA reductase – short biological half-time ~ 2 h):
   feed-back repression of HMG-CoA synthesis: **cholesterol**
   LDL-CH - liver, periferal cells
   CHR-CH – liver

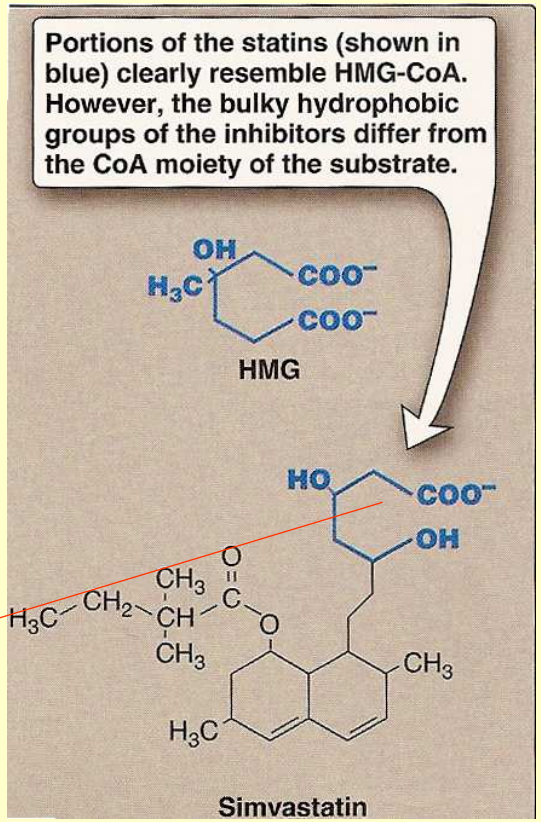
2. Hormonal regulation: insulin - enzyme dephosphorylation = **activation**, enzyme expressior
   glukagon - enzyme phosphorylation - **inactivation**

Control of cholesterol synthesis

3. Competitive inhibition of HMG CoA reductase:

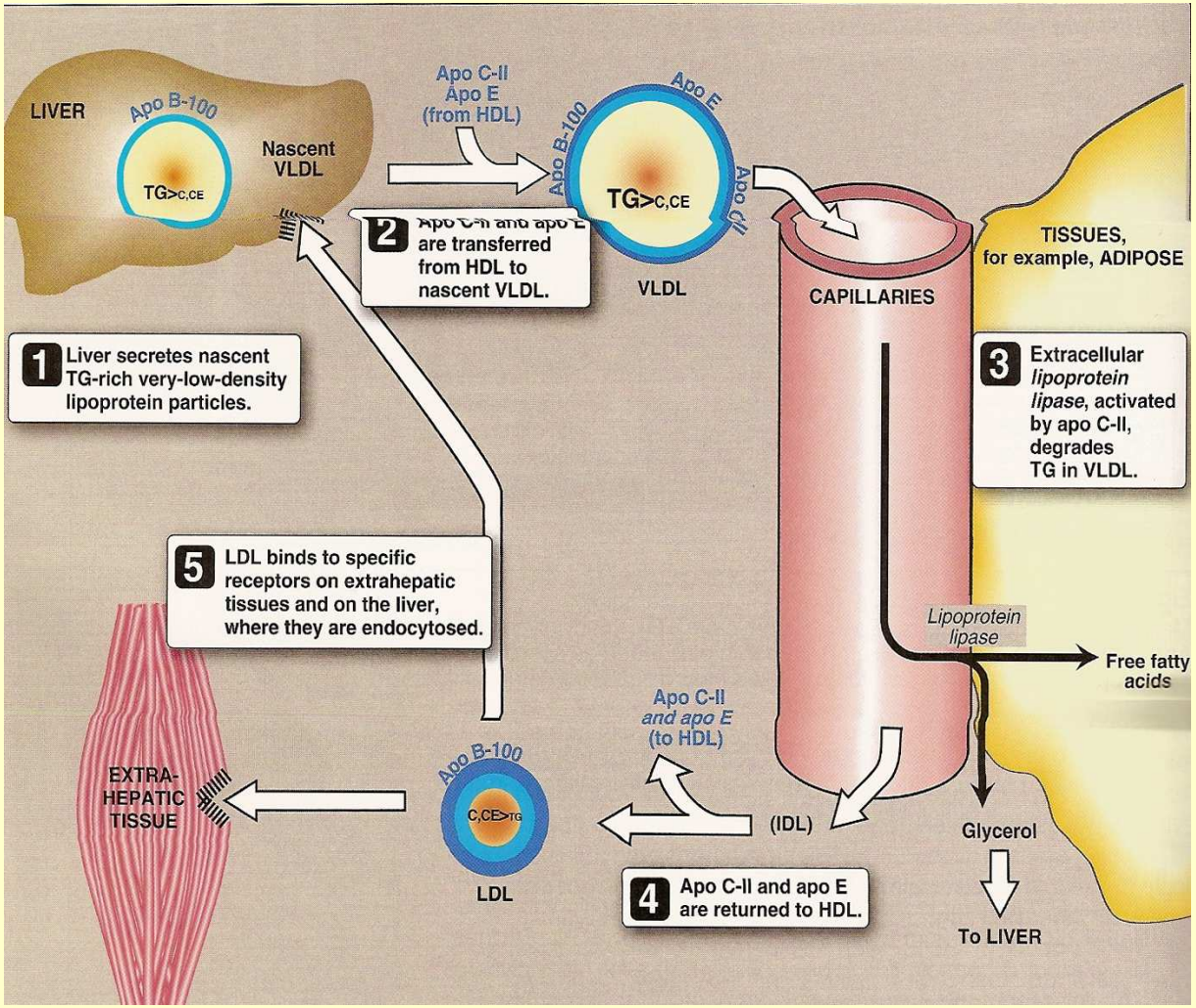
statins – fungal compounds or chemically synthesized therapeutic agents of similar structure-

lovastatin
mevastatin
simvastatin
} treatment of hypercholesterolemia



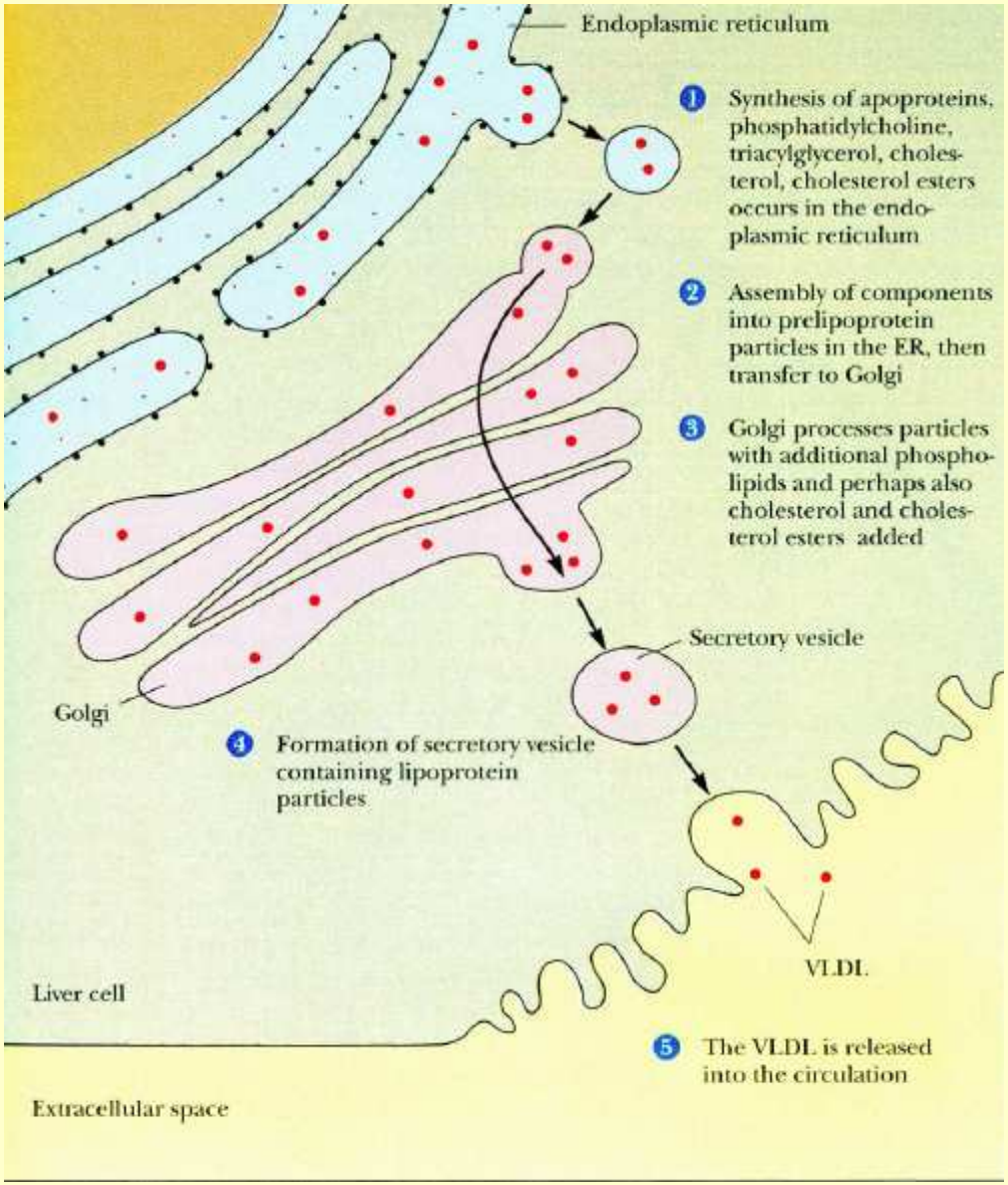
binding to the active site of HMG CoA reductase

Metabolism of VLDL- and LDL-cholesterol

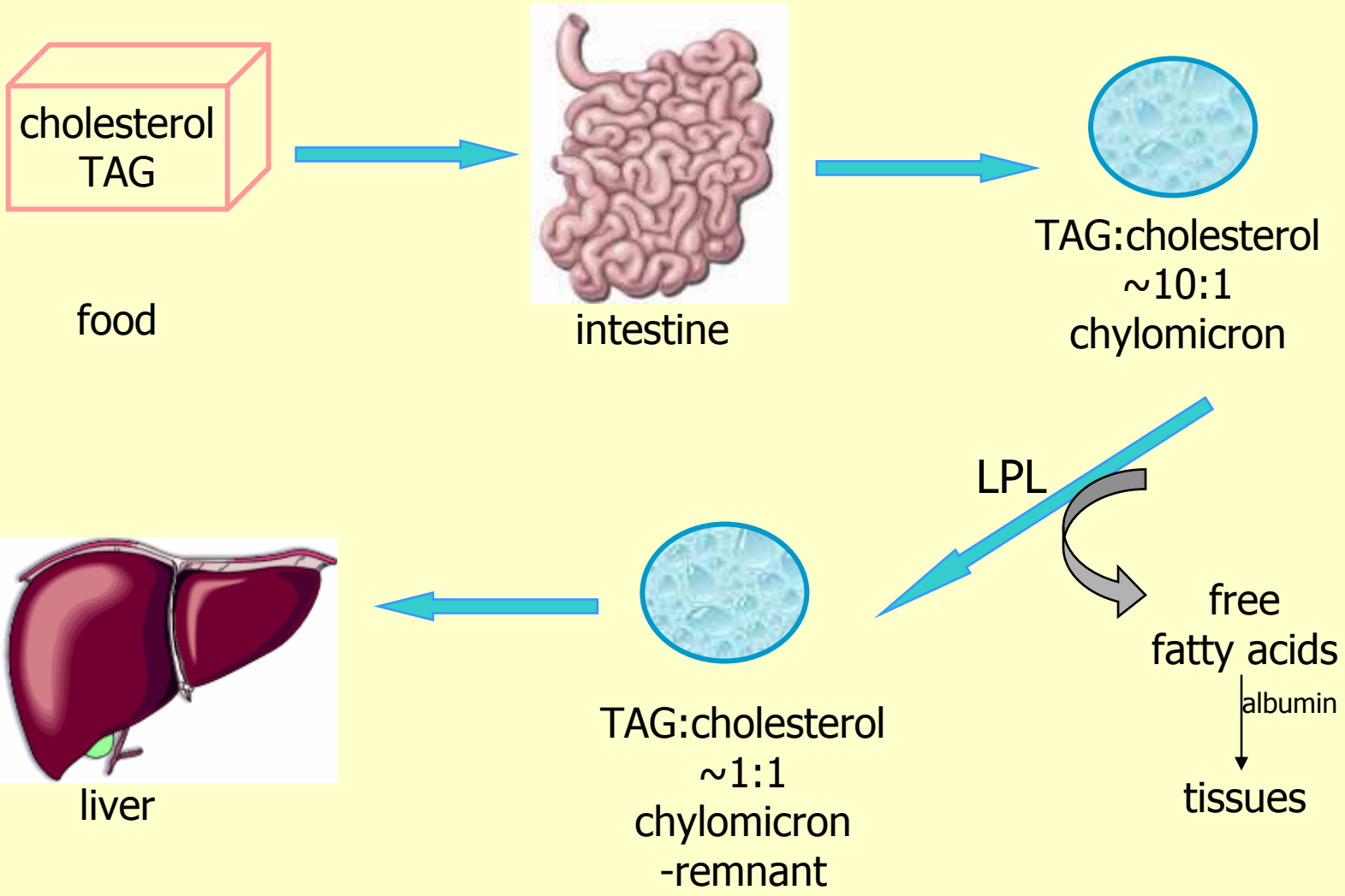


- Synthesized cholesterol packed into VLDL, VLDL converted in plasma to IDL and LDL
- LDL deliver cholesterol to periferal tissues via LDL receptors
- IDL and ~75 % of LDL return back to liver, are degraded in lysosomes
- Released cholesterol incorporated into VLDL or converted to bile acids

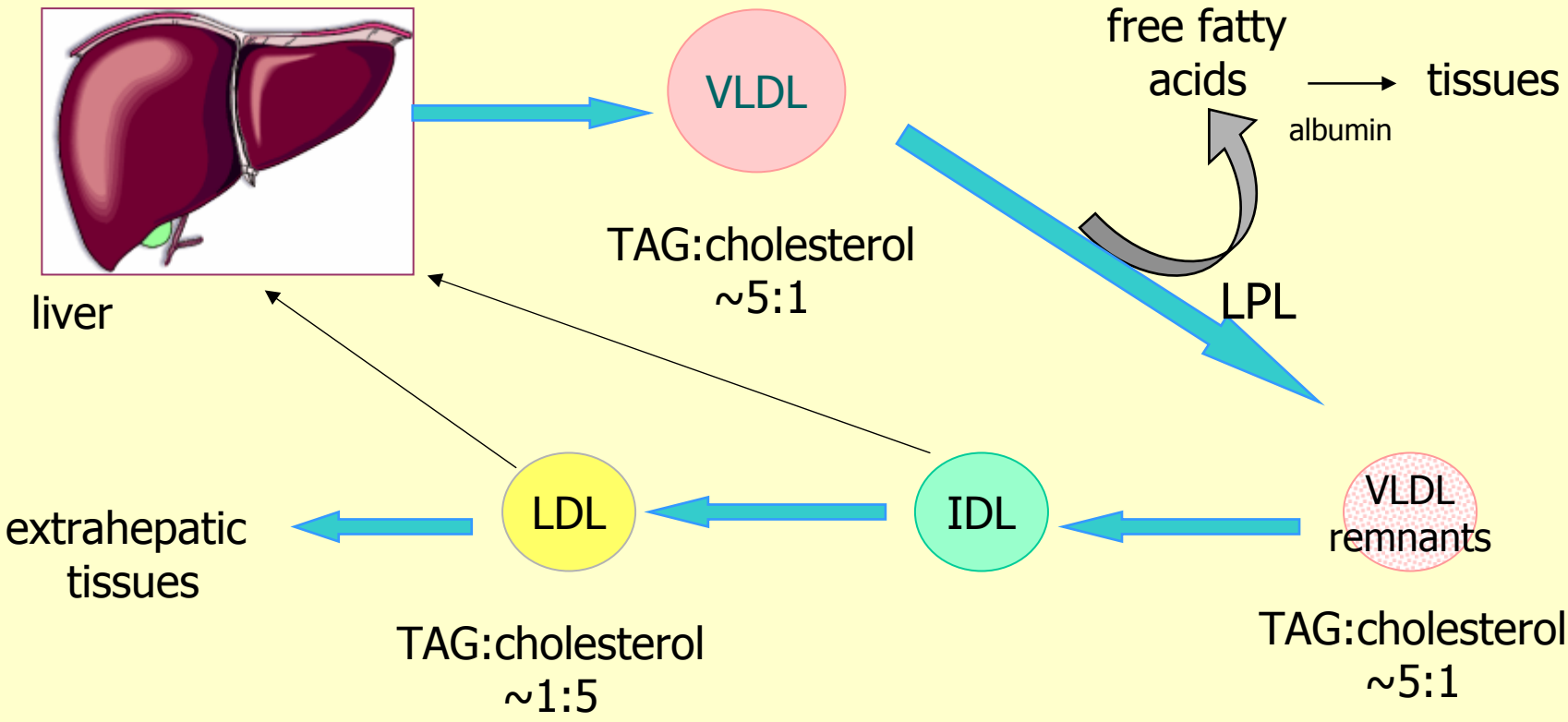
Secretion of VLDL from the liver



Transport of exogenous cholesterol



Transport of endogenous cholesterol



LDL-receptor

- provides cholesterol delivery into tissues
- membrane glycoprotein
- requires **apoB**, apoE as ligands for interaction with a lipoprotein particle

defective LDL-receptor

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↑ LDL in plasma

↓

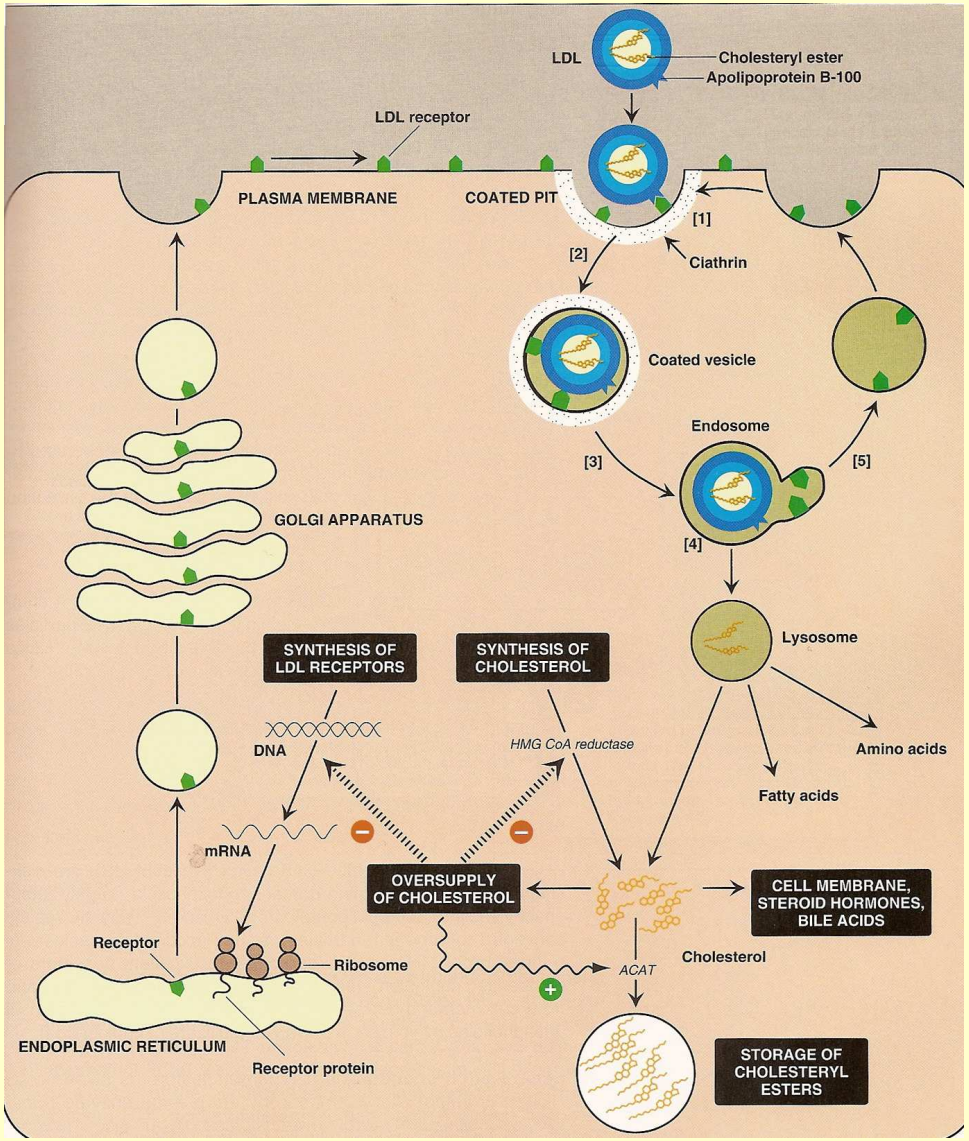
↑ plasma cholesterol

↓

hypercholesterolemia

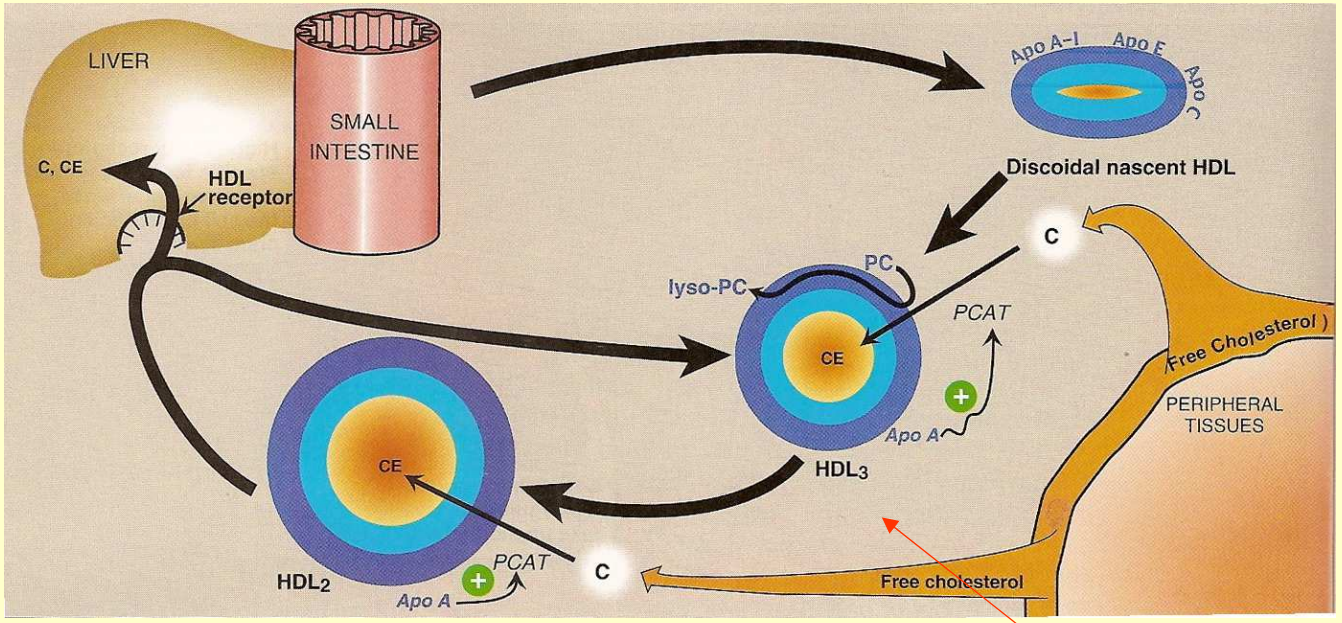
↓

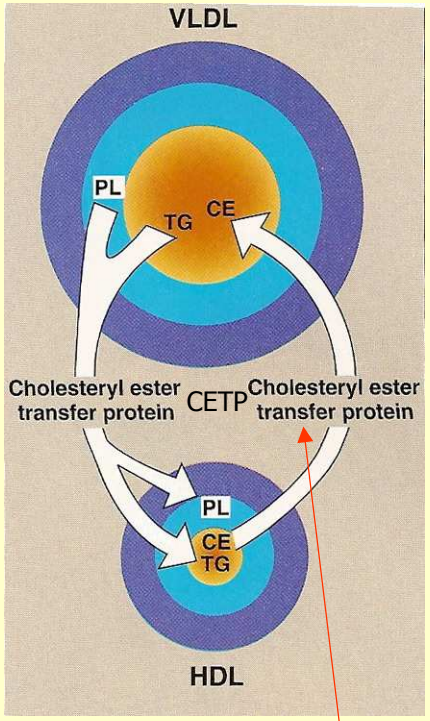
atherosclerosis
(hypercholesterolemia IIa)



LDL uptake by endocytosis → lysosomal digestion → cholesterol (and other products) release into cell

Metabolism of HDL





PCAT = phosphatidylcholine:cholesterol acyltransferase
(LCAT = lecithin:cholesterol acyltransferase)

reverse cholesterol transport

- HDL pick up cholesterol from periferal tissue and other lipoproteins
- cholesterol is esterified by **LCAT**, particles fill with cholesteryl esters → **HDL_3**
- HDL_3 transfers cholesteryl esters to VLDL in exchange for TAG - transfer is mediated by CETP
- particles accept apoCII from VLDL, apo E from IDL → **HDL_2**
- **HDL_2** are taken up by liver via specific receptors, endocytoced and digested in lysosomes
- cholesterol released into liver cell is incorporated into VLDL or converted to bile acids

Hypercholesterolemia

= elevated level of cholesterol in the blood

– primary (genetic) – defective LDL-receptor

- secondary – diet high in fat and cholesterol, obesity, alcoholism, diabetes mellitus.....

risk factor of atherosclerosis, associated with the formation of atherosclerotic plaques

↑LDL atherogenic

↑ HDL protective