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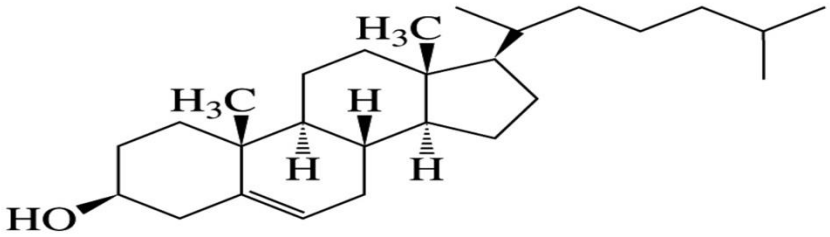
Cholesterol



cholesterol

F.A. for esterification

this is the cholesterol and it contains 27 carbons

17c in the four rings

2c methyl groups

1 hydroxyl group and it is the only hydrophilic site in the molecule All the cells that contains acetyl coA coenzyme can synthesize cholesterol In different proportions and the liver is the highest organ to synthesize cholesterol 58%

It is important in the body as a building block of cells and many hormones but within limits

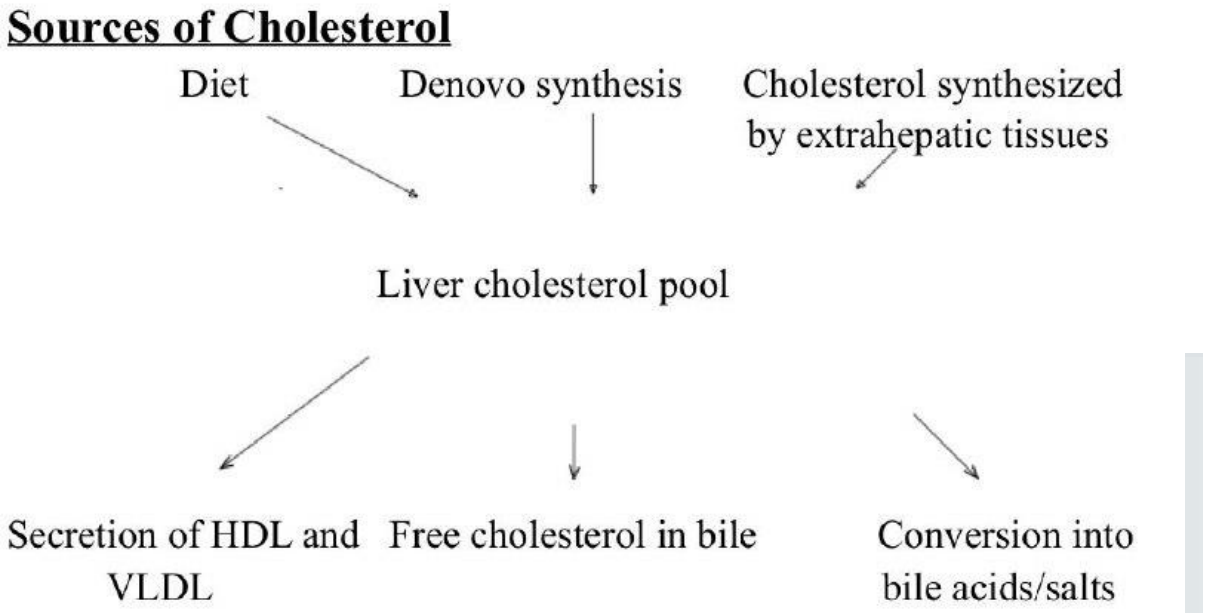
Cholesterol

- It is the principal sterol synthesized from simpler substances by animals, but small quantities are synthesized in other eukaryotes, such as plants and fungi but almost completely absent among prokaryotes, which include bacteria.
- Although cholesterol is an important and necessary molecule for animals, a high level of serum cholesterol is an indicator for diseases such as heart diseases and arteriosclerosis
- Cholesterol is recycled, excreted by the liver via the bile into

the digestive tract, then, about 50% of the excreted cholesterol is reabsorbed through enterohepatic circulation to liver again.

- Phytosterols (plant sterols) can compete cholesterol

reabsorption in intestinal tract back into the intestinal lumen for elimination



Cholesterol is excreted by bile acids —> large intestine —> bacterial flora convert cholesterol into two compounds called(neutral sterols)

50% of cholesterol is reabsorbed through enterohepatic circulation——> back into the liver

Bile is divided into two fractions :

1-fluid fraction (phospholipid and bile pigments)

2-solid fraction (cholesterol itself)

In the two cases if inequlebrium happens between the solid fraction and the soluble fraction precipitation will occur

1-decreased cholesterol/ bile pigment precipitation

2-decreased bile pigment /cholesterol precipitation—> bile stones.

So there should be equilibrium between bile acids and cholesterol.

We have another type of sterol we call it :

Ergosterol

It is more absorbed more than cholesterol.

Also ergosterol is eliminated from the body because we don't have that convert it to another compound.

Functions

1- Cholesterol is required to build and maintain membranes; it regulates membrane fluidity (reducing the permeability of

the plasma membrane to protons (H+ and Na+).

2- Within the cell membrane, cholesterol also functions in intracellular transport, cell signaling, formation of lipid rafts in the plasma membrane and nerve conduction

providing insulation for more efficient impulses conduction.

3- Some researches indicate that cholesterol may act as an antioxidant.

4- Cholesterol is essential for the structure and function of caveola and clathrin -coated pits for endocytosis

Coated pits : site on the cell membrane contains receptors for different enzymes.

which can be investigated by using methyl β-cyclodextrin (MβCD) to remove cholesterol from the plasma membrane

5- Within cells, cholesterol is the precursor molecule in several biochemical pathways:

A-In the liver, cholesterol is converted to bile acids and bile salts to solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins (A,D,E and K).

B- Cholesterol is an important precursor molecule for the synthesis of vitamin D3.

C- All the steroid hormones are synthesized from Cholesterol

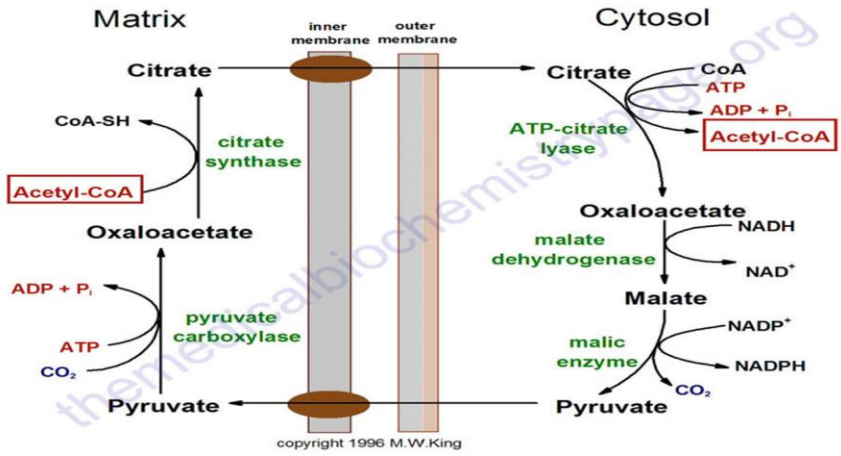
Cholesterol synthesis

- Similar to ketogenic pathway

- Occurs in cytosol and it is highly regulated

- The whole process is very energy-dependent in terms of ATP and NADPH.

- 80 % in liver, ~10% intestine, ~5% skin



-liver cells which synthesize Ketone bodies synthesize about (80-90)% of cholesterol

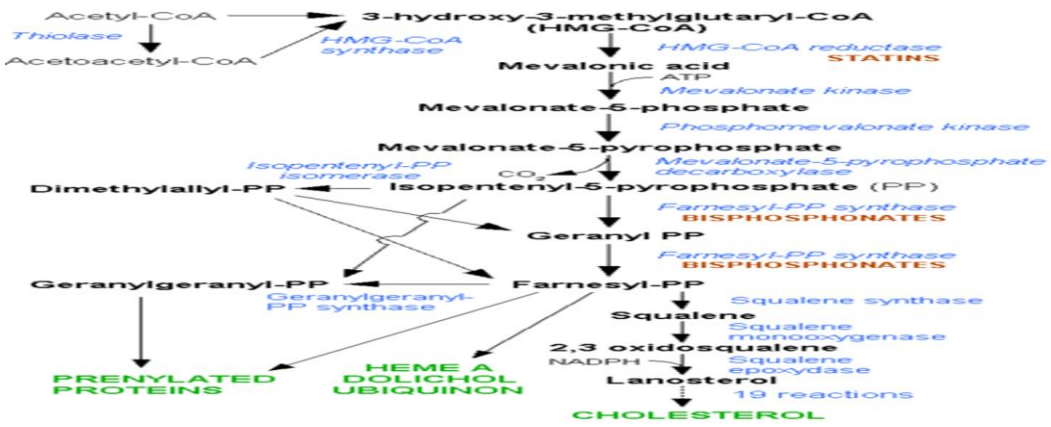
These cells contains two isozymes in the same cell:

1-mitochondrial type—>ketogenesis

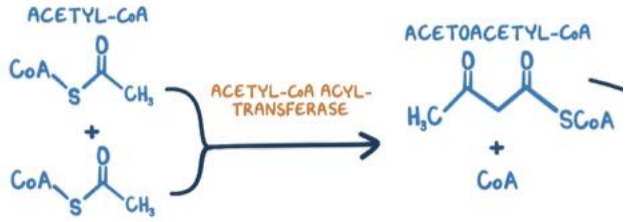
2-cytosolic type ——>cholesterol synthesis

The rate limiting step occurs at HMG-CoA) reductase.

- Intermediates in the pathway are used for the synthesis of prenylated proteins, dolichol, coenzyme Q and the side chain of heme a.

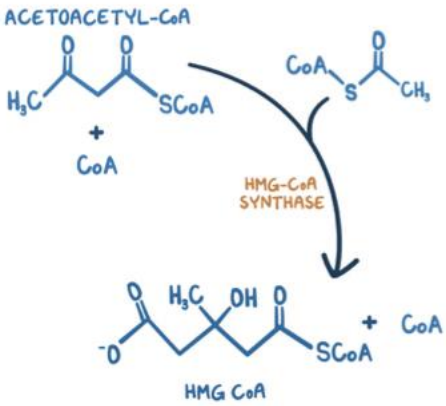


The reactions with better illustrations and figures :

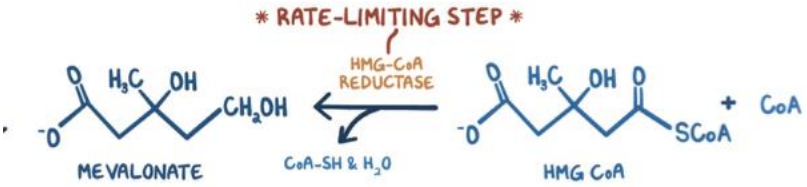


The first two reactions are the same reactions in the ketogenesis.

HMG coA synthase has to isozymes one in the mitochondria and the



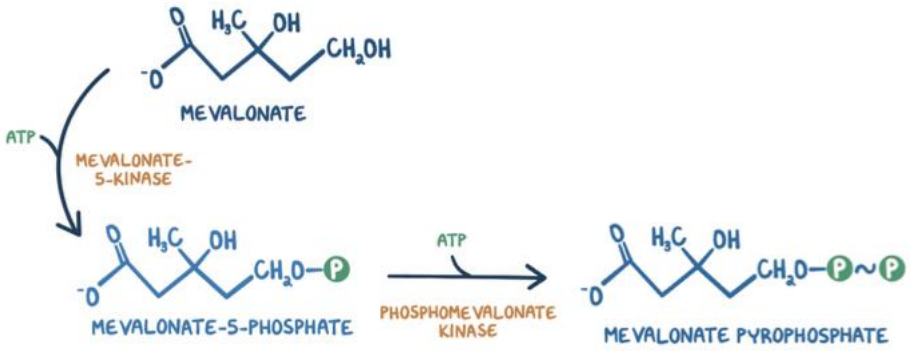
other in the cytoplasm.



This a rate limiting step.

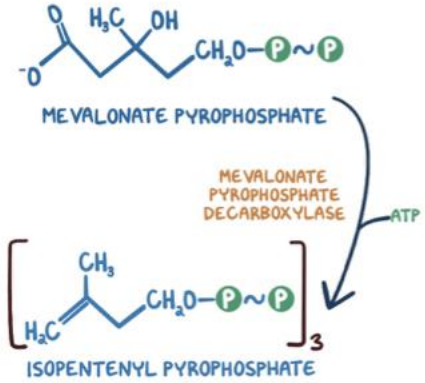
This enzyme is the key regulatory enzymeIt is inhibited by statins (competitive inhibitor).

Reducing equivalent in this reaction is NADPH+H .



The mevalonate is activated by mevalonate 5-kinase into mevalonate 5-phosphate

Then another phosphate convert it into mevalonate pyrophosphate.



Decarboylase enzyme will take one carbon from mevalonate pyrophosphat and convert it into isopentyl 5- pyrophosphate (5 carbon compound).

Untile this step how many acetyl coA have been consumed ?

2 acetyl coA

Part of this compound is converted into dimethyleallyle pyrophosphate by isomerase enzyme

Then isopentyle pyrophosphate is combined with dimethyleallyle pyrophosphate and this give us geranylepyrophosphate.

How many acetyl coA have been consumed until this step?

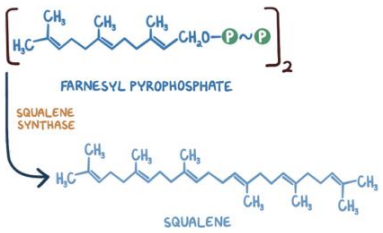
4 acetyl coA.

Two with the isopentyl pyrophosphate and two with the dimethylallyle pyrophosphate

—Then another dimythelallyle pyrophosphate is added to gerenyle pyrophosphate to give us a compound composed of 15 carbon atoms called farnesyle pyrophosphate.

How many acetyl coA have been consumed until this step?

6 acetyl coA



then another molecule of farnesyle pyrophosphate is added to give us a 30 carbon molecule called

Squalene

How many ATP molecules are consumed to synthesise one cholesterol molecule?

Every 5 carbon molecule ————->2ATP

~132 ATP molecules

NADPH ————> we use it in reducing reactions

It is not used / it isn't the reducing equivalent

— Another inhibitor of cholesterol synthesis at the two steps that it is catalyzed by farnesyle pyrophsphate synthase enzyme ——-> bisphosphonate and it is used as antihypercholestrolemic drug.

— Farnesyle-pp and geranylgeranyl-pp are intermediate giving end products before reaching the cholesterol

Farnesyl pp gives :

1-heme A which enters the cytochrome AA3 of the electron transport chain

2-ubiquinon —> coenzyme Q —->ETC

3-Prenylated proteins —>protective proteins by prenylated group from fat and it is also produced by the geranylgeranyl-pp

Regulating Cholesterol Synthesis

- Normal cholesterol level in the body (150 - 200 mg/dl) is maintained primarily by controlling the level of de novo synthesis which is regulated in part by the dietary intake of cholesterol.

- The cellular supply of cholesterol is maintained at a steady level by three distinct mechanisms:

1- Regulation of HMGR activity and levels

2- Regulation of excess intracellular free cholesterol through the activity of acyl-CoA cholesterol acyltransferase, ACAT

- The function of this enzyme is to add acyle group into the hydroxyl group in the cholesterol thus trapping it inside the cells.

3- Regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL-mediated reverse transport.

It is regulated by VLDL which is converted in the blood to LDL

And the remaining cholesterol is transported to the liver by the HDL.

When the liver synthesize good VLDL and HDL it can control the amount of cholesterol that is transferred to extrahepatic tissues and the return back of the extra cholesterol from the peripheral tissues into the liver.

Regulation of HMGR activity:

It is carried out by four mechanisms:

1- Feed-back inhibition

2- Rate of enzyme degradation

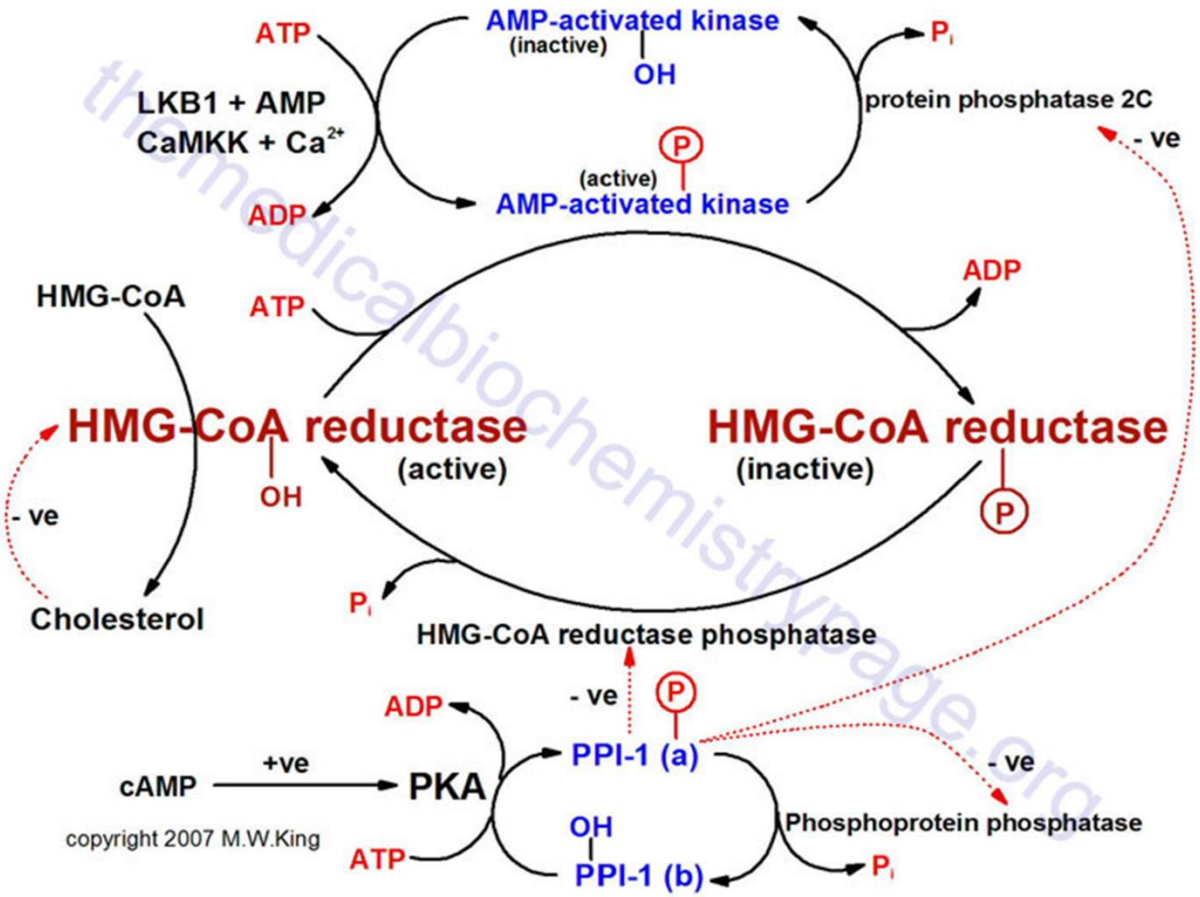
3- Control of gene expression (long term)

4- Phosphorylation –dephosphorylation (short term)

المحرك لهذول كلهم هو الكوليسترول

- The first three control mechanisms are exerted by cholesterol itself where it acts as a feed-back inhibitor of pre-existing HMGR as well as inducing rapid degradation of the enzyme as a result of cholesterol-induced polyubiquitination of HMGR and its degradation in the proteosome.

- In addition, when cholesterol is in excess the amount of mRNA for HMGR is reduced due to the decrease in expression of gene.



We start from the middle from the rate limiting enzyme (HMG-reductase)

The difference between the two enzymes is that the right one is inactive(phosphorelated) an the left one is active(dephosphorelated)

- Adding phosphate group leads to the inhibition of the enzyme.
- The enzyme that Perform the inactivation is the AMP-activated kinase enzyme (this enzyme is active when phosphate group is added to it)

- The phosphate group will be added to the two enzymes at the same time one of them will be activated (AMP-activated kinase enzyme) and the other one will be inactivated (HMG-coA reductase enzyme)
- LKB1 or c3 kinase11 & caMKK ——–-> activate AMP-activated kinase enzyme by phosphorylation
- This enzyme is inhibited by protein phosphatase —> takes the phosphate group from this enzyme ——>thus keeping the HMG-reductase in its active dephosphorylated form

- HMG-coA reductase phosphatase enzyme works immediately on the HMG-coA reductase after phosphate group has been added to it and if the cells in need for The activated HMG-coA reductase enzyme it takes of the phosphate group from it

- This phosphatase enzyme is regulated by protein phosphatase inhibitor-1 (this enzyme function is nearly the same as AMP-activated kinase as it is active (when phosphorylated) and inactive(when dephosphorylated) and it is phosphorylated by the protein kinase Under the effect of the level of cAMP (hormonal regulation) as the level of cAMP is increased by GLUCAGON.

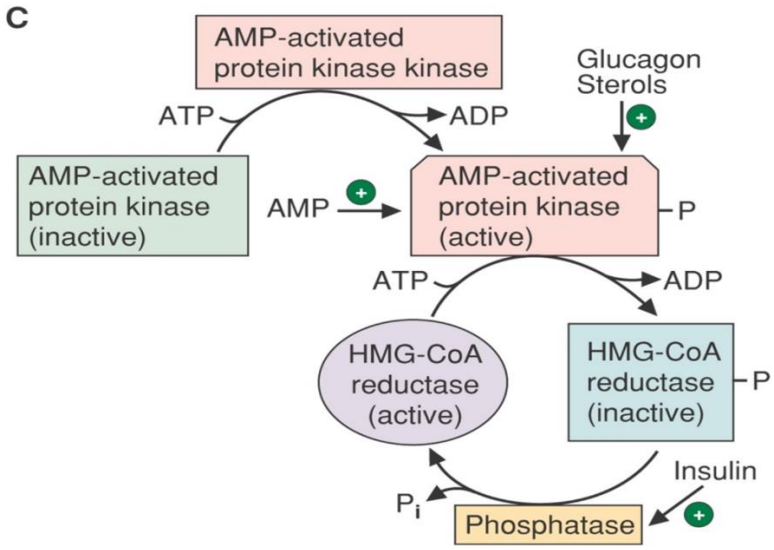
- cAMP —>. Activate protein kinase A ——> activate protein phosphatase inhibitor -1 by its phosphorylation and once it's activated it cause inhibition of three enzymes at the same time

1-HMG-coA reductase phosphatase

2-phosphoprotein phosphatase

3-protein phosphatase

Closes all the bathways to stop HMG coA reductase.



- The intracellular level of cAMP is regulated by hormonal stimuli, so, regulation of cholesterol biosynthesis is hormonally controlled.

- Insulin leads to a decrease in cAMP, which in turn activates cholesterol synthesis.

- Alternatively, glucagon and epinephrine, which increase the level of cAMP, inhibit cholesterol synthesis.

-Long-term control of HMGR activity is exerted primarily through control over the synthesis and degradation of the enzyme.

-When levels of cholesterol are high, the level of expression of the HMGR gene is reduced, while, reduced levels of cholesterol activate expression of the gene.

- Insulin also brings about long-term regulation of cholesterol metabolism by increasing the level of HMGR synthesis

The main regulatory mechanism

- It is the sensing of intracellular cholesterol in the endoplasmic

reticulum by the protein SREBP (sterol regulatory element-binding protein 1 and 2, mainly the type 2).

- In the presence of cholesterol, SREBP-2 is bound to two other proteins: SCAP (SREBP-cleavage-activating protein) and Insig-1.

- When cholesterol levels fall, Insig-1 dissociates from the SREBP-2-SCAP complex, allowing the complex to migrate to golgi apparatus, where SREBP-2 is cleaved by S1P and S2P (site-1 and -2 proteases), two enzymes that are activated by SCAP when cholesterol levels are ↓.

- The cleaved SREBP then migrates to the nucleus and acts as a transcription factor to bind to the SRE (sterol regulatory element) to activate transcription of genes for HMG-CoA Reductase and

LDL receptor and other enzymes in cholesterol synthetic pathway

The cleavage occurs at two stages

First stage : cleavage of insi1 protein under the effect of sterol sensing domain

Second stage : scap protein under the effect of site1-2 protease

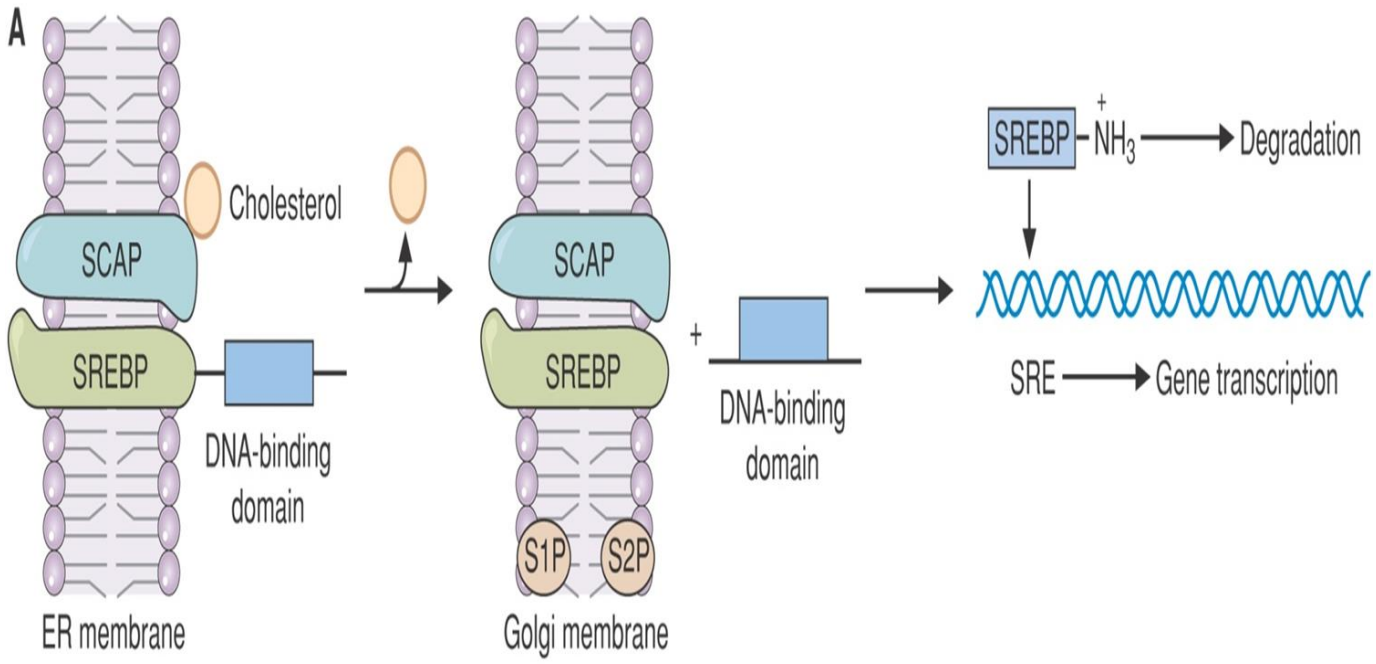
—-> releasing the SREBP which migrates from the Golgi apparatus to the nucleus

—->hormone response element —> increase rate of expression of HMG coA reductase enzyme.

-The former scavenges circulating LDL from the bloodstream, whereas HMG-CoA reductase leads to an increase of endogenous

production of cholesterol.

- SREBP pathway regulates expression of many genes that control lipid formation and metabolism and body fuel allocation.



Proteolytic Regulation of HMG-CoA Reductase

- The stability of HMGR is regulated as the rate of flux through the mevalonate synthesis pathway changes.

When the flux is high the rate of HMGR degradation is also high.

When the flux is low, degradation of HMGR decreases.

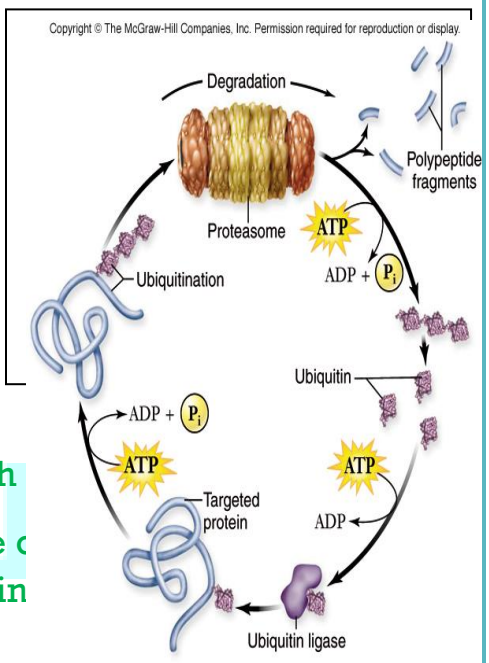
HMGR is localized to the ER and like SREBP contains a sterol-sensing domain, SSD.

The degradation of HMGR occurs within the proteosome (a multi-protein complex dedicated for protein degradation).

The primary signal directing proteins to the proteosome is ubiquitination followed by degradation of HMGR.

Ubiquitin is a 7.6 kDa protein that is covalently attached to proteins targeted for degradation by ubiquitin ligases

- These enzymes attach multiple copies of ubiquitin allowing for recognition by the proteosome.
- The primary sterol regulating HMGR degradation is cholesterol itself.



Which stimulate the ligases to bind the ubiquitin with

Sensing domain in the HMG coA reductase when the c
levels is high it! Stimulate Ligase to degrade ubiquitin
proteins into small fragments.

The main causes of hypercholesterolemia include:

1- High fats and carbohydrates diet
2- lack of exercise
3- Obstructive jaundice
4- obesity
5- Hypothyroidism

(associated with **hypocholestremia** —>due to increased secretion of thyroid hormones (which are anabolic under normal conditions) and under abnormal pathological conditions they are catabolic—->degrading proteins of the body.

T3/T4 activates hydroxylase which convert cholesterol into bile acids and bile salts.

Primary bile acids are (choline acid , hydroxy chalice acid) and both have more hydroxylation

More hydroxylation of cholesterol more producing of bile acids and more consuming of cholesterol.

6- smoking

7- Familial hypercholesterolemia

8- excessive coffee drinking

What is the physiology jaundice ?

Occurs At birth ,because of immaturity of the liver and immaturity of erythrocytes because the membrane of erythrocytes is weak so it is easily damaged releasing the HG which is processed into bilirubin

The most important two forms of jaundice is hepatic(is associated with hypocholestremia) jaundice and obstructive jaundice (associated with hypercholesterolemia)

- Total cholesterol (total-C) is defined as the sum of HDL-C, LDL-C, and VLDL-C.

- Usually, only the total-C, HDL-C, and triacylglycerols are measured.

- VLDL is usually estimated as one-fifth of the triglycerides and the LDL is estimated using the Friedewald formula:

LDL-C= [total-C] − [(HDL-C)+(estimated VLDL-C)].

- Direct LDL measures are used when triacylglycerols level is about 400 mg/dl with more error when triacylglycerols level is higher than 400 mg/dl.

Hypocholesterolemia

- It is an abnormally low levels of cholesterol

- Some studies suggest a link with depression, cancer and cerebral hemorrhage and hypocholesterolemia.

- Classified into: primary and secondary hypocholesterolemia

A- Primary hypocholesterolemia: its main causes are:

1- Tangier disease, a rare autosomal recessively inherited disorder characterized by the absence or severe deficiency of HDL in plasma.

2-

2- Familial hypobetalipoprotienemia, an autosomal dominant disorder of apo-B metabolism, is associated with marked hypocholesterolemia (<50 mg/dl in homozygotes) with Low LDL, cholesterol, TG but normal HDL.

3- Abetalipoproteinemia, a rare autosomal recessive disorder caused by a deficiency of MTP (microsomal triglyceride transfer protein) which resulted in a absence of the apo-B-containing lipoproteins in the plasma.

B- Secondary hypocholesterolemia: its main causes are:

1- Severe chronic hepatic insufficiency diseases

2- Hyperthyroidism 3- Fever 4- Trauma

5- Digestive malnutrition (congenital and acquired)

6- Malignancy (as acute myelogenous leukemia)

7- Inflammatory disease (RA, SLE) 8- Depression illness.

يا رب السّلام أنت السلام
وإليك يعود السلام
هبنا سلاماً نعبر به

ما تبقى من الطريق💙

• د. كفاح أبو هنّود.