Cholesterol

F.A. for esterification

Cholesterol

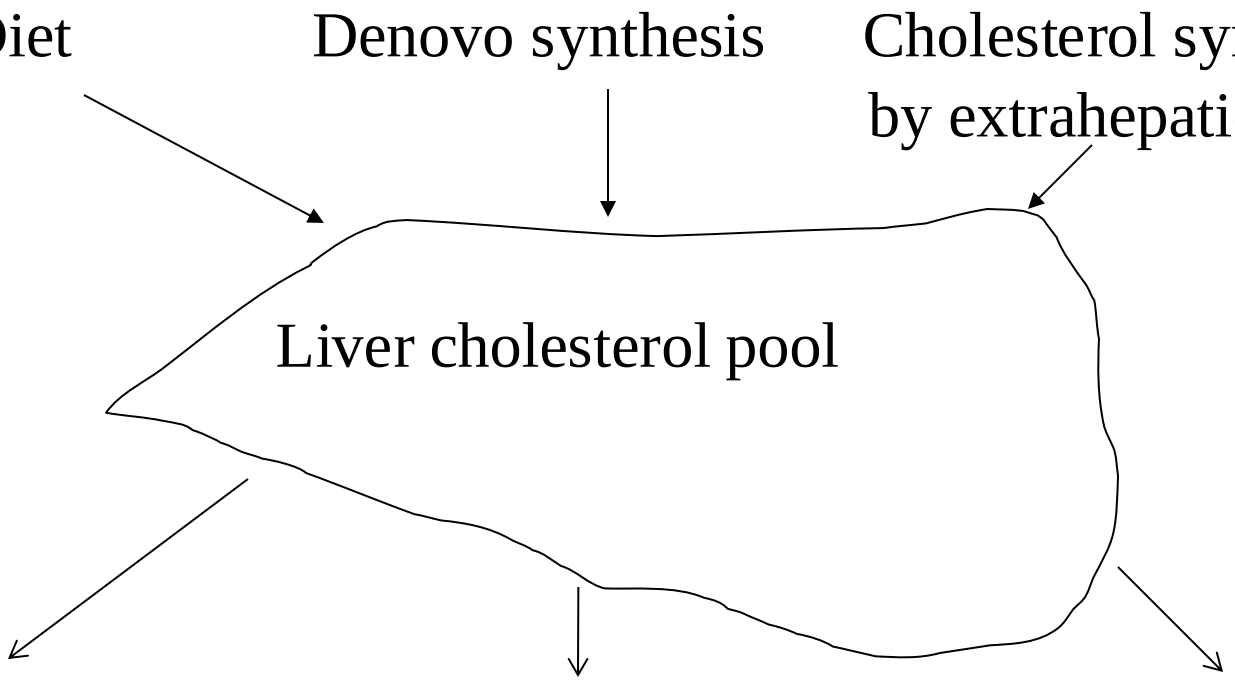
- It is the principal sterol synthesized from simpler substances by animals, but small quantities are synthesized in other eukaryotes, such as plants and fungi but almost completely absent among prokaryotes, which include bacteria.

- 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.

Sources of Cholesterol



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 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:

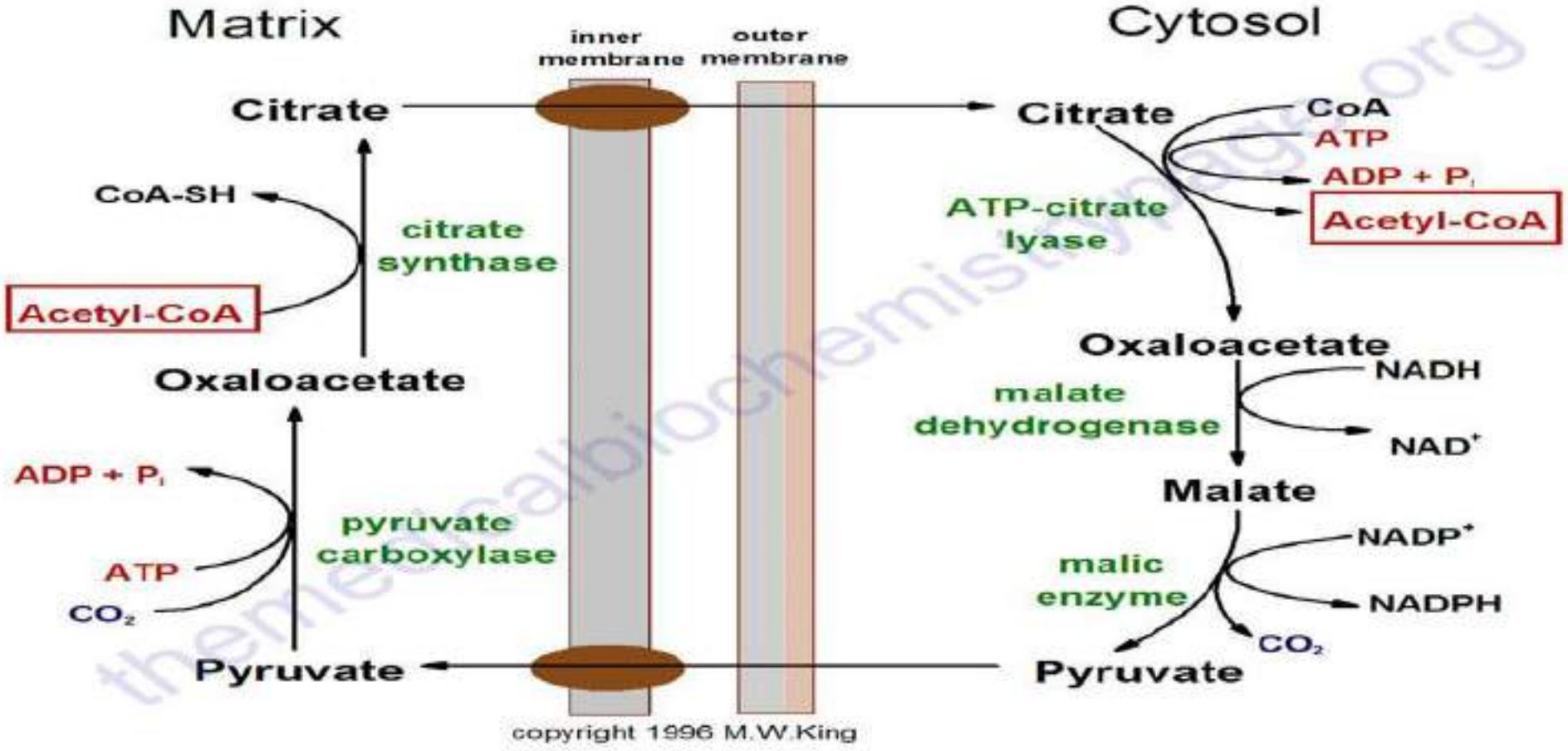
A-In the liver, cholesterol is converted to bile acids and bile salts to solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins (A,D,E and K).

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

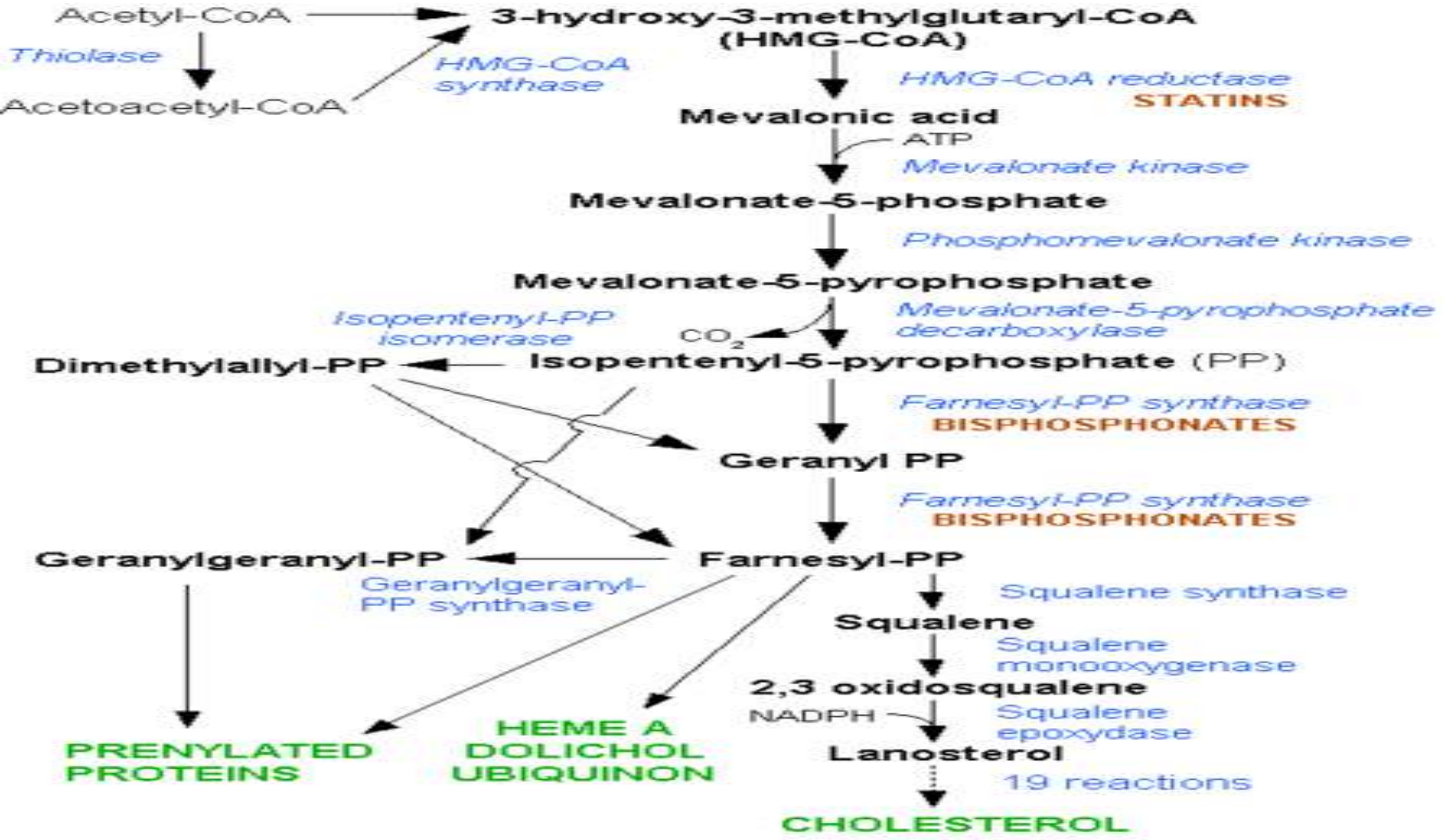
C- All the steroid hormones are synthesized from cholesterol.

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



- 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*.



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

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

Regulation of HMGR activity:

It is carried out by four mechanisms:

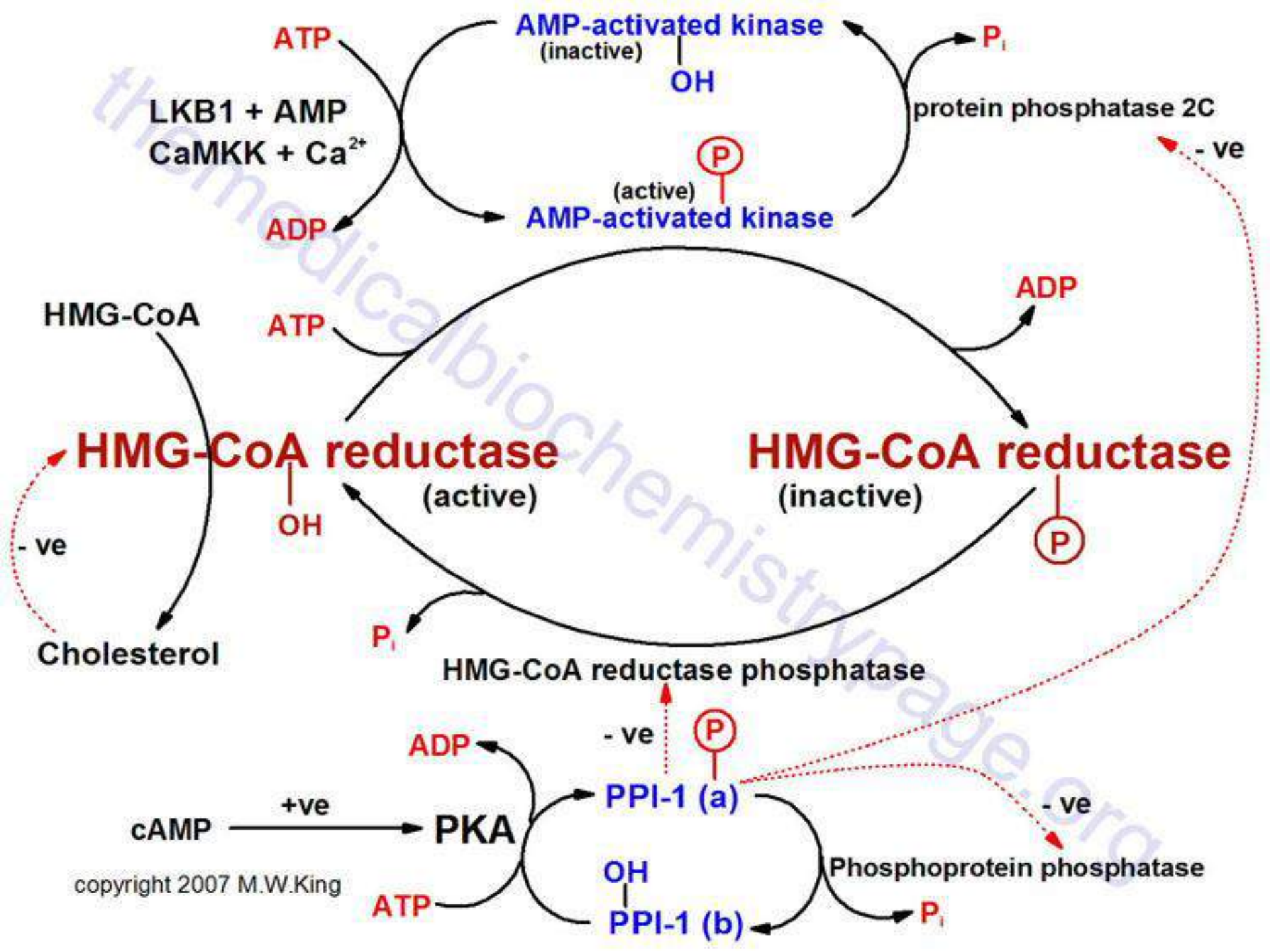
1- Feed-back inhibition

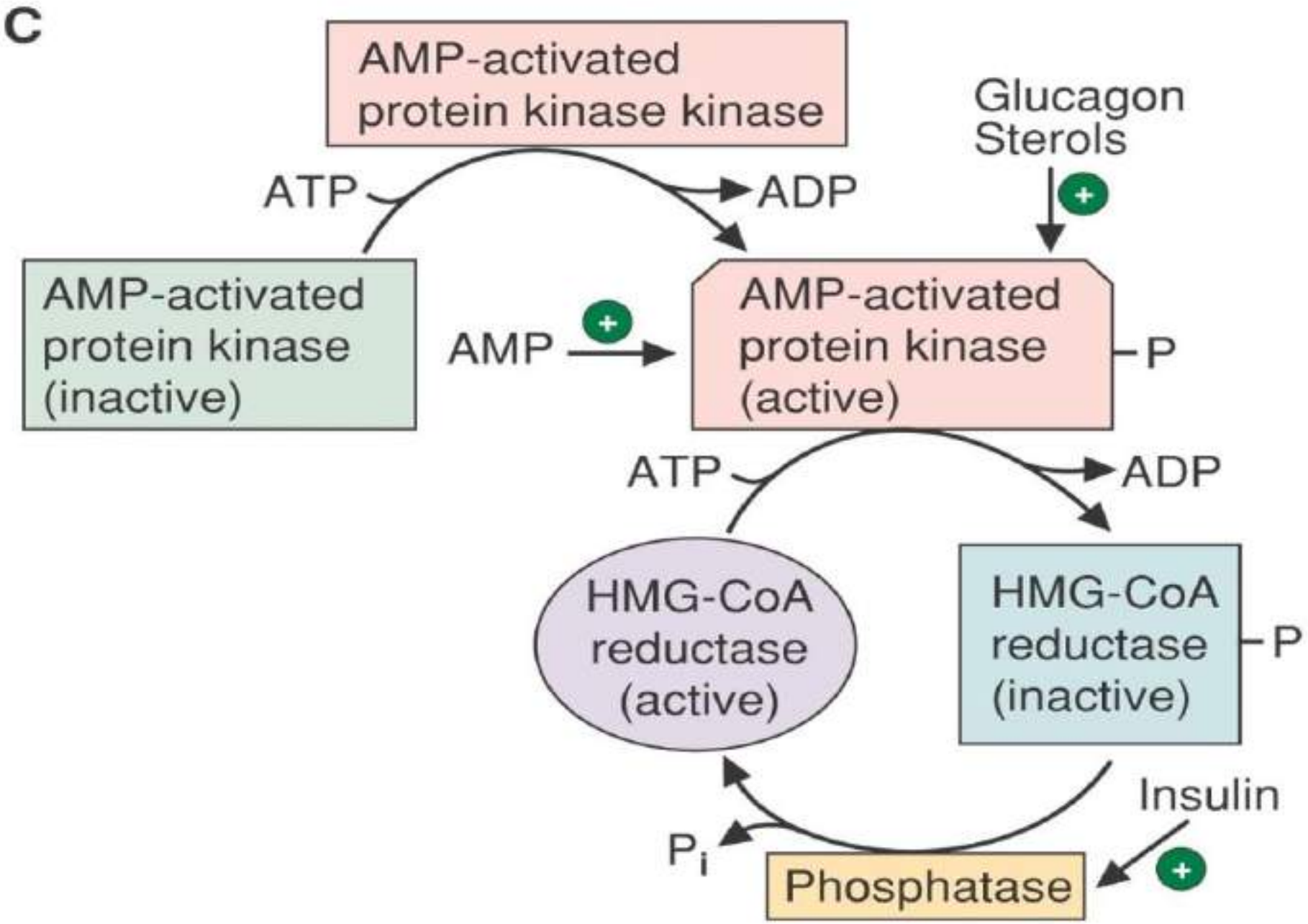
2- Rate of enzyme degradation

3- Control of gene expression (long term)

4- Phosphorylation –dephosphorylation (short term)

- 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.




C
AMP-activated protein kinase kinase
ATP
ADP
Glucagon
Sterols
+
AMP-activated protein kinase (inactive)
AMP
+
AMP-activated protein kinase (active)
P
ATP
ADP
HMG-CoA reductase (active)
HMG-CoA reductase (inactive)
P
Insulin
+
P_i
Phosphatase

- 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.

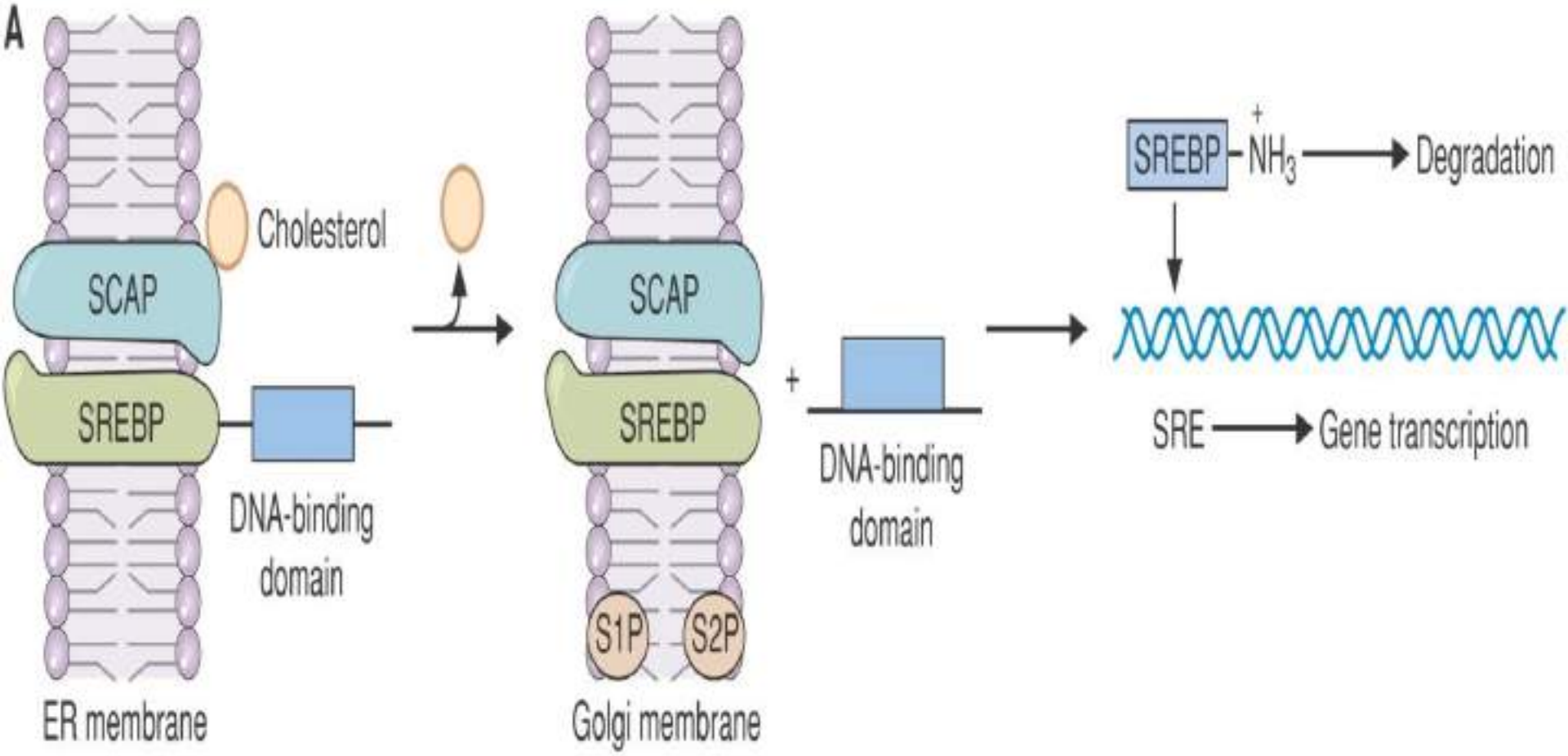
The main regulatory mechanism

- 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 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.



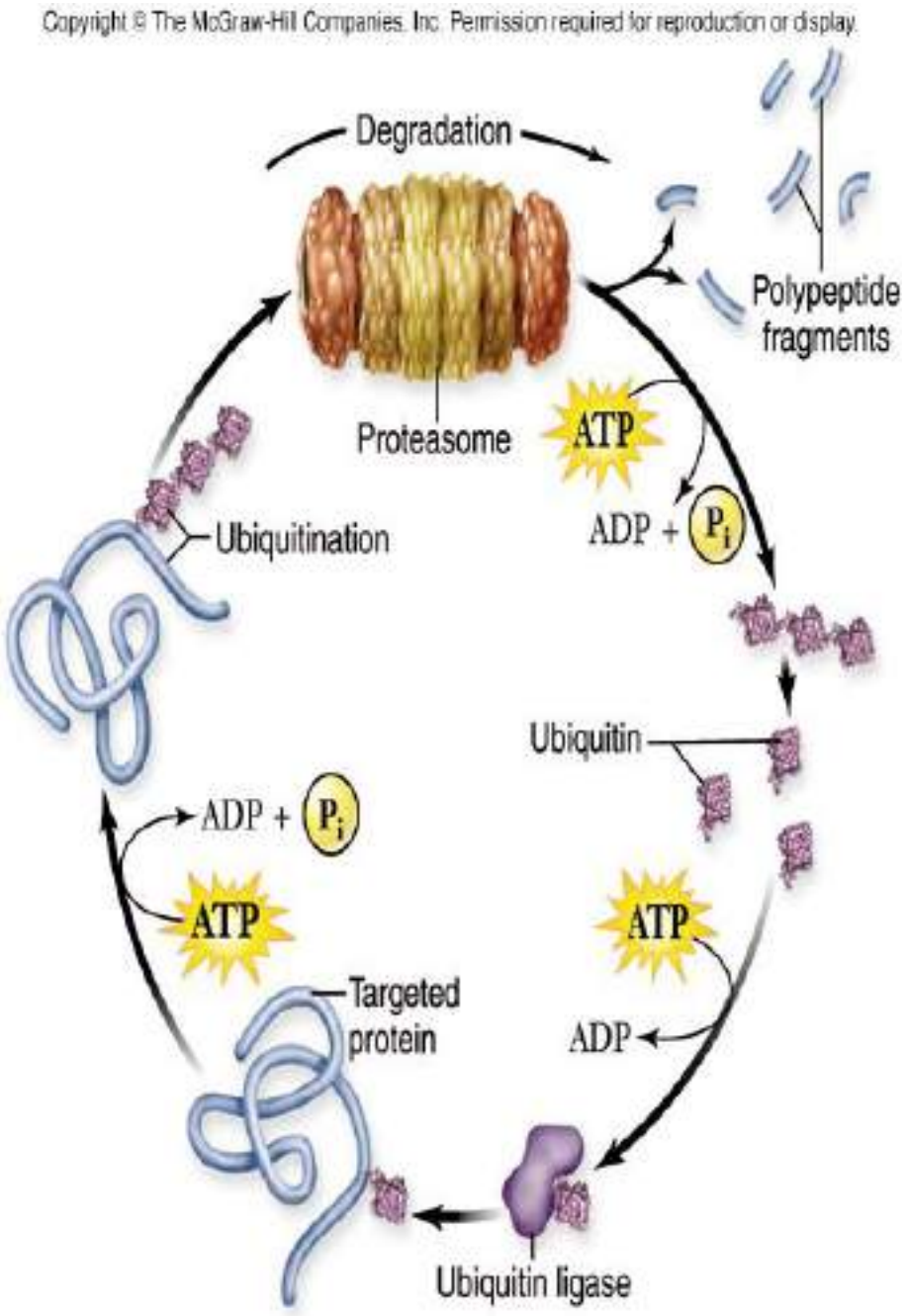
Proteolytic Regulation of HMG-CoA Reductase

- 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.

The main causes of hypercholesterolemia include:

1- High fats and carbohydrates diet 2- lack of exercise
3- Obstructive jaundice
4- obesity
5- Hypothyroidism 6- smoking
7- Familial hypercholesterolemia
8- excessive coffee drinking



- 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- <u>Primary hypocholesterolemia</u>: 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- 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- <u>Secondary hypocholesterolemia</u>: 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