Bryan Krantz: University of California, Berkeley
MCB 102, Spring 2008, Metabolism Lecture 14
Reading: Ch. 21 of *Principles of Biochemistry*, "Lipid Biosynthesis."

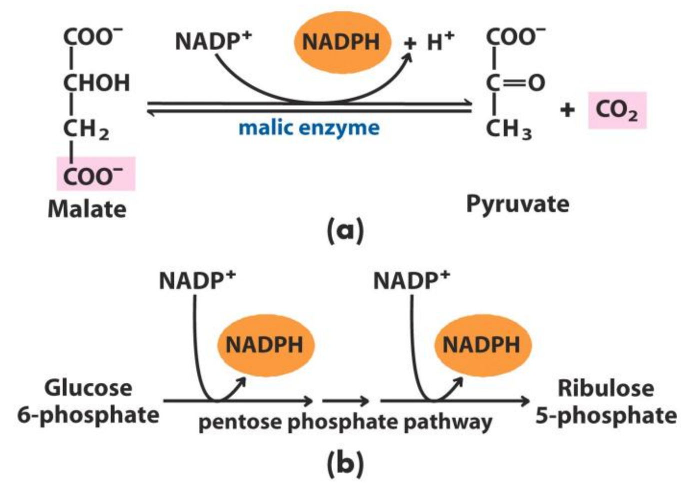
Energy Requirements for Fatty Acid Synthesis

For C_{16} palmitic acid starting with Acetyl-CoA and a generous pool of NADPH:

7 ATP to charge Acetyl-CoA → Malonyl-CoA

14 NADPH for the reductions of C=C and C=O bonds

A lot of energy is required to make a fatty acid.



Why?

● Fatty Acids are made in the cytosol and NAD^+ is favored 10^5-fold more than NADH there.

● By having largely separate cytosolic NADPH and mitochondrial NADH pools, anabolic pathways do not draw on the pools needed to produce ATP (by Ox. Phos.)

How?

● Mainly, pentose phosphate pathway.

● Malic enzyme may be used to steal reducing equivalents from the mitochondria (but this is a secondary pathway).

Acetyl-CoA requirements for Fatty Acid Synthesis are also high

● For a C_N fatty acid there are N/2 Acetyl-CoA required.

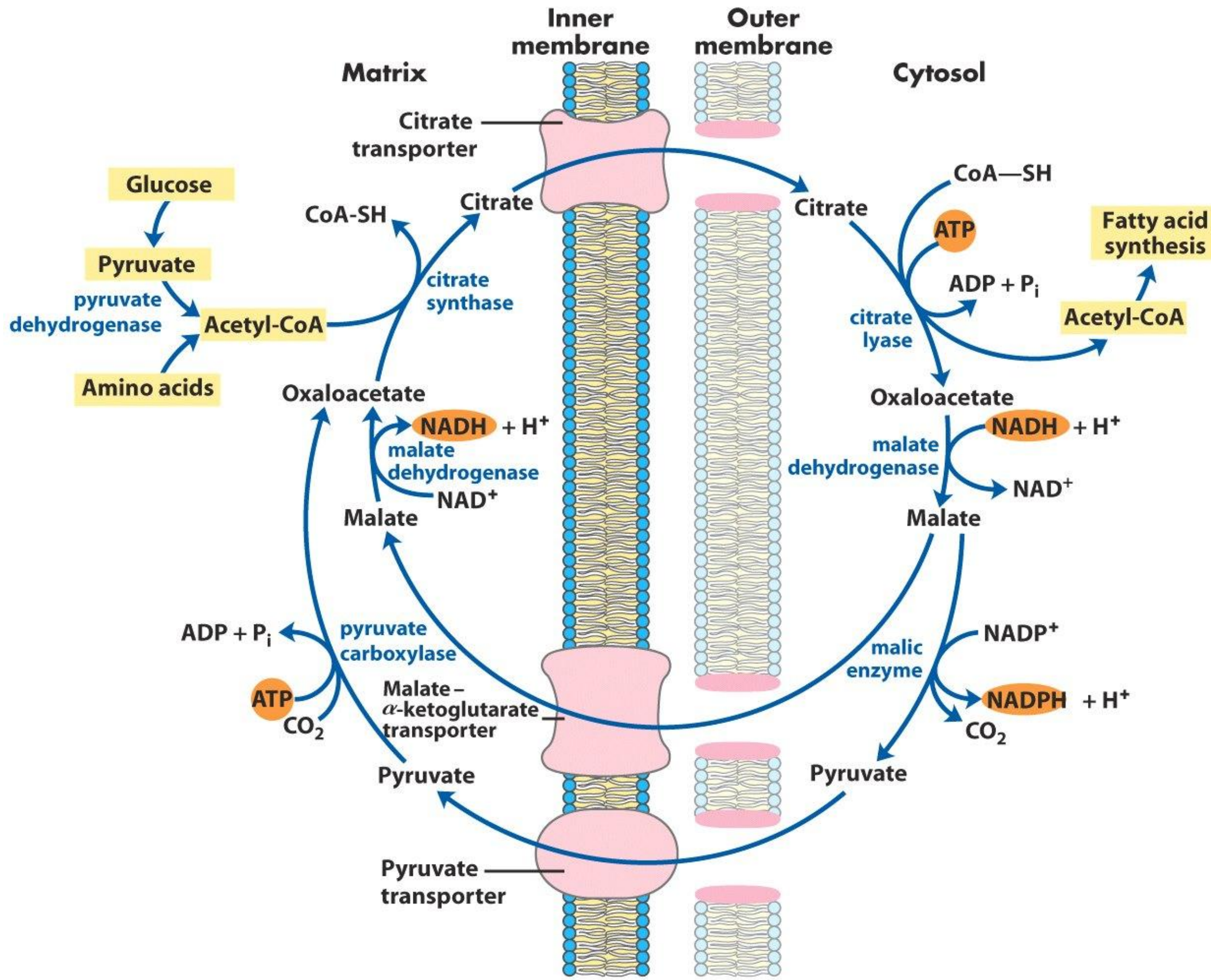
● Acetyl-CoA comes from pyruvate dehydrogenase and fatty acid oxidation (inside mitochondria).

● Citrate must be pumped out of mitochondria and cleaved using 1 ATP. There is a **citrate lyase** in the cytosol to break the citrate into Acetyl-CoA and oxaloacetate but it costs ATP.

*****So starting from citrate the process cost 1 additional ATP per Acetyl-CoA*****

➔ There are a lot of transport steps summarized in the following figure [on left].

➔ Know also that a high sugar meal will kick in **insulin**, and insulin upregulates Citrate



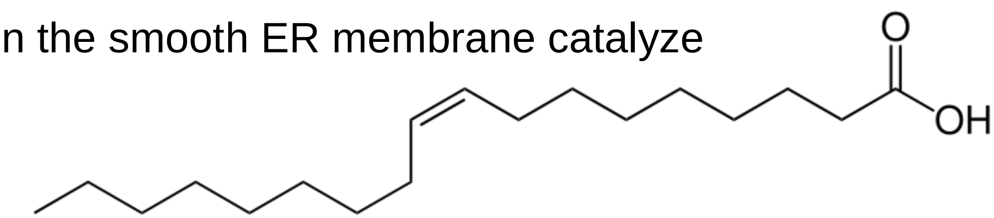
Lyase, which leads to fatty acid synthesis, turing all those sweets into fat.

Unsaturated Fatty Acids

● We need unsaturated fatty acids to maintain the fluidity of the membrane.

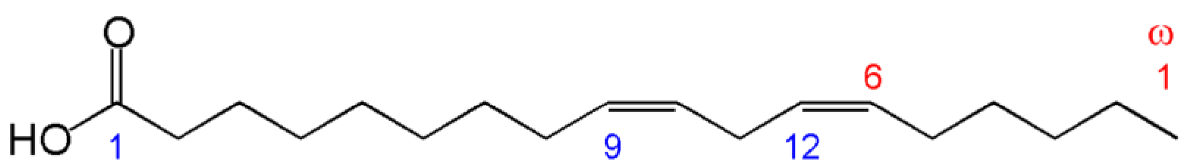
● This is done using an enzyme called **desaturase**.

● Electron transfer reactions to cytochromes in the smooth ER membrane catalyze desaturation.



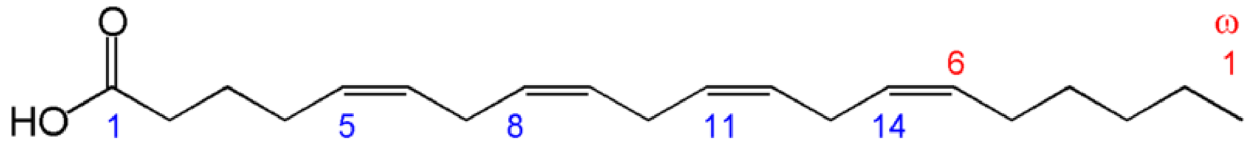
Essential Fatty Acids

● We cannot make all desaturations and so some required unsaturated fatty acids are required from diet, e.g., **linoleate**, which we get from plants.



● Linoleate ($\Delta^{9,12}$) with two double bonds, or linolineate ($\Delta^{9,12,15}$) with three double bonds

● Linoleate, for example, gives rise to **arachidonic acid**, which is a C_{20} fatty acid that is made by elongation of linoleate. It forms four double bonds. Arachidonic acid is used in the generation of local signals like **prostaglandin**, which are important for inflammation.

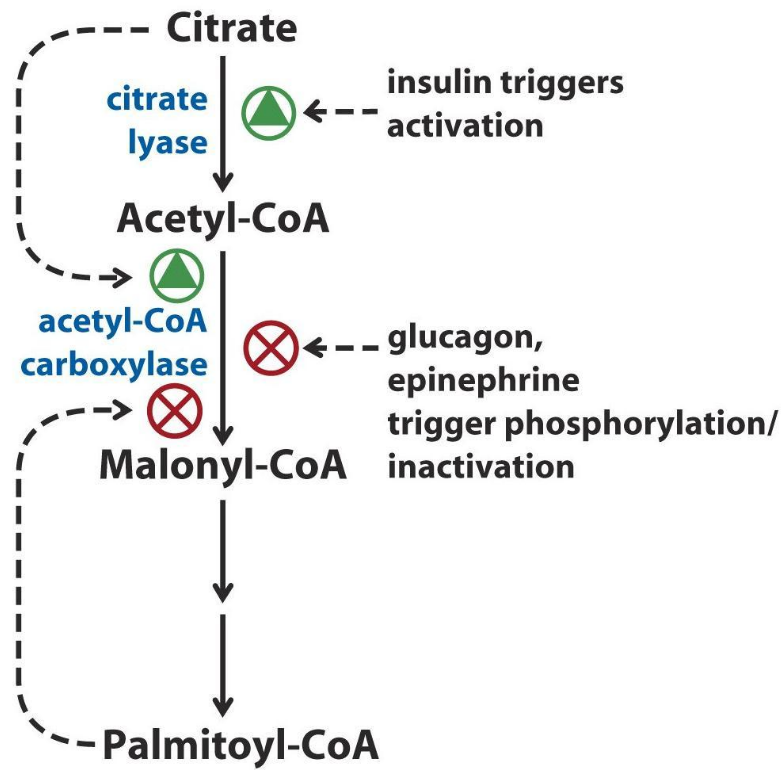

HO
O
1
5
8
11
14
6
ω
1

Regulation of Fatty Acid Biosynthesis & Degradation.

● The regulated / committed step is the generation of **malonyl-CoA**. Once you generate malonyl-CoA, you use it purely for fatty acid biosynthesis.

● **Malonyl-CoA synthetase** is the enzyme that gets phosphorylated by the cAMP cascade.

→If liver cells are stimulated by the presence of glucagon/epinephrine, then malonyl-CoA synthetase gets phosphorylated. When it gets phosphorylated, its activity is then inhibited.



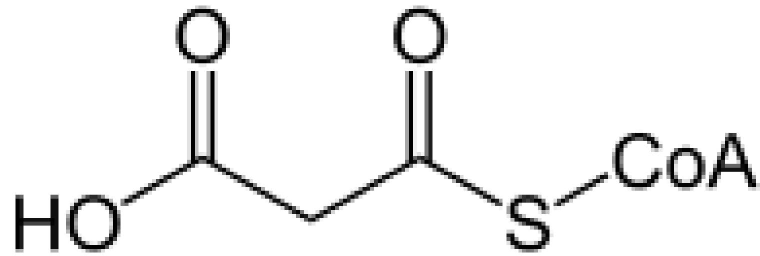
Allosteric regulation of malonyl-CoA synthetase

● When the sugar level in your blood is high, insulin is present, then the liver tends to get rid of that glucose by activating glycolysis and generating acetyl-CoA and citrate.

● Citrate & acetyl-CoA activate malonyl-CoA synthetase, and fatty acid biosynthesis becomes activated.

Allosteric regulation of Fatty Acid Degredation by Malonyl-CoA

● If fatty acid synthesis and degredation were to continue simultaneously then a futile cycle would develop, which wastes energy.

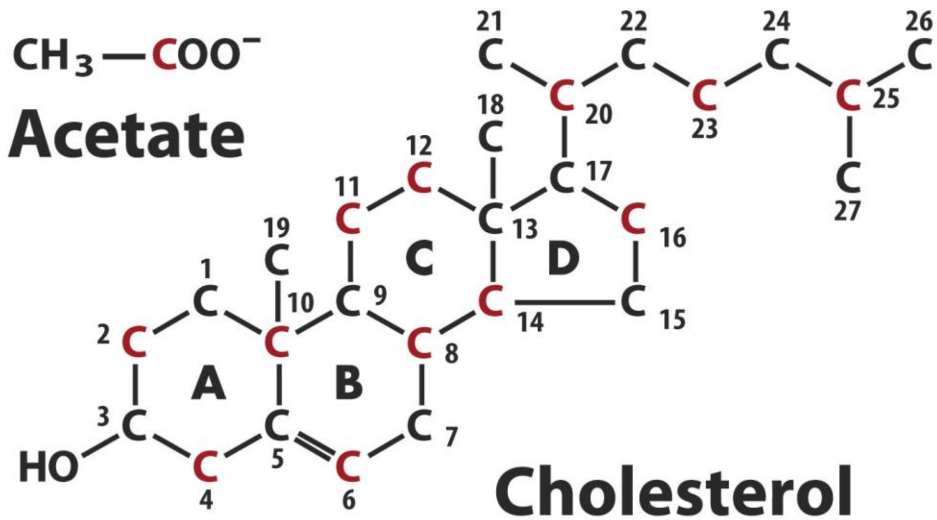


● BUT β oxidation is inhibited by malonyl-CoA, because transport via carnitine cannot occur, as the **carnitine acyl-transferase** activity is inhibited by malonyl-CoA.

● Compartmentalization of synthesis and degredation supports well this type of control mechanism.

Cholesterol Biosynthesis

● People are worried about eating cholesterol due to a relationship to coronary heart disease.



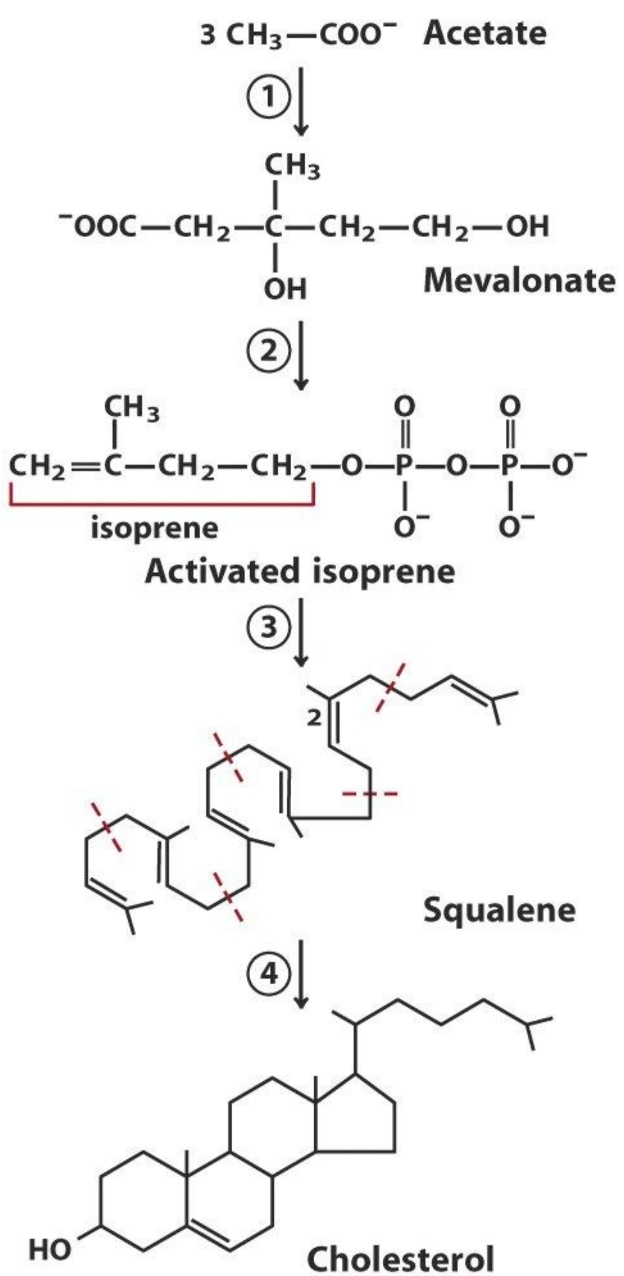
● Dietary restrictions of cholesterol intact does not solve this problem, since we make most of the cholesterol in our bodies (~70% on average).

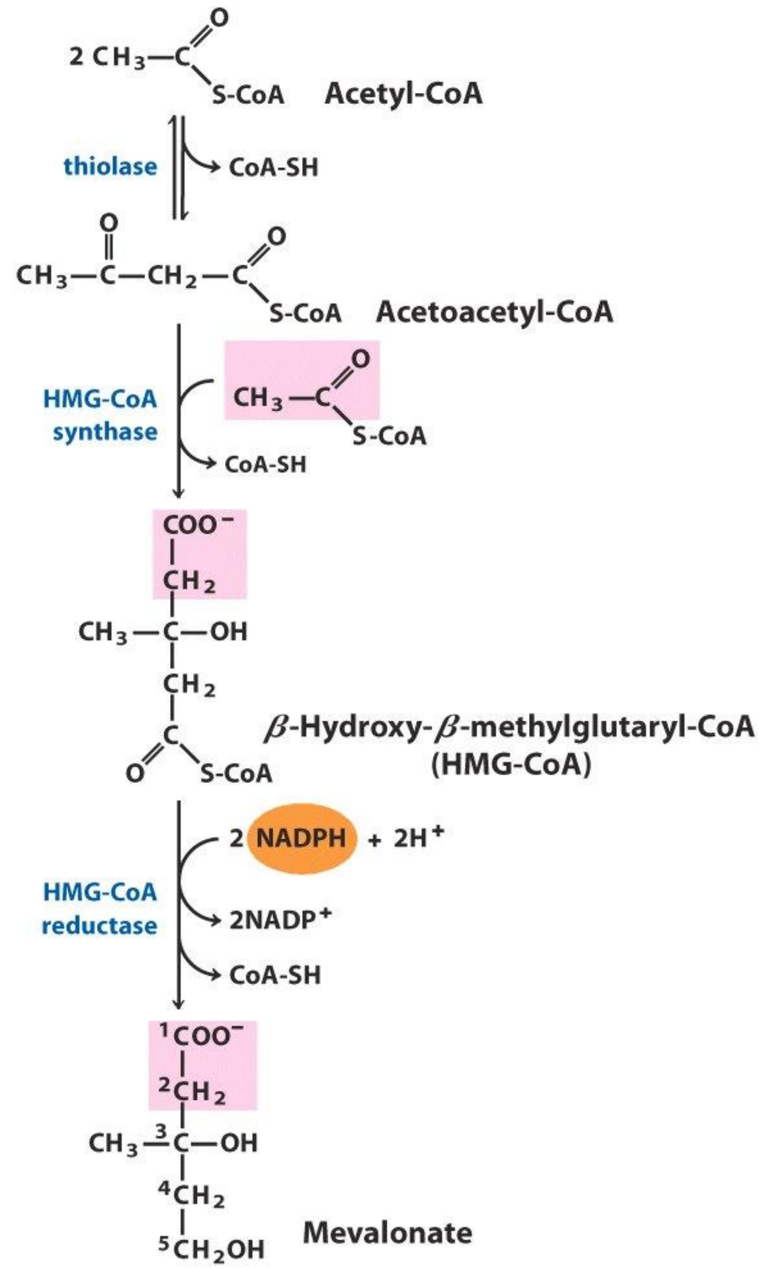
● We need cholesterol: it maintains membrane fluidity and forms the basic skeleton for steroids and hormones.

● From the looks of it, you may think that this must come from a lot of different carbon skeletons. Nope.

● *All* the carbon in cholesterol come from Acetyl-CoA.

Biosynthesis of Cholesterol





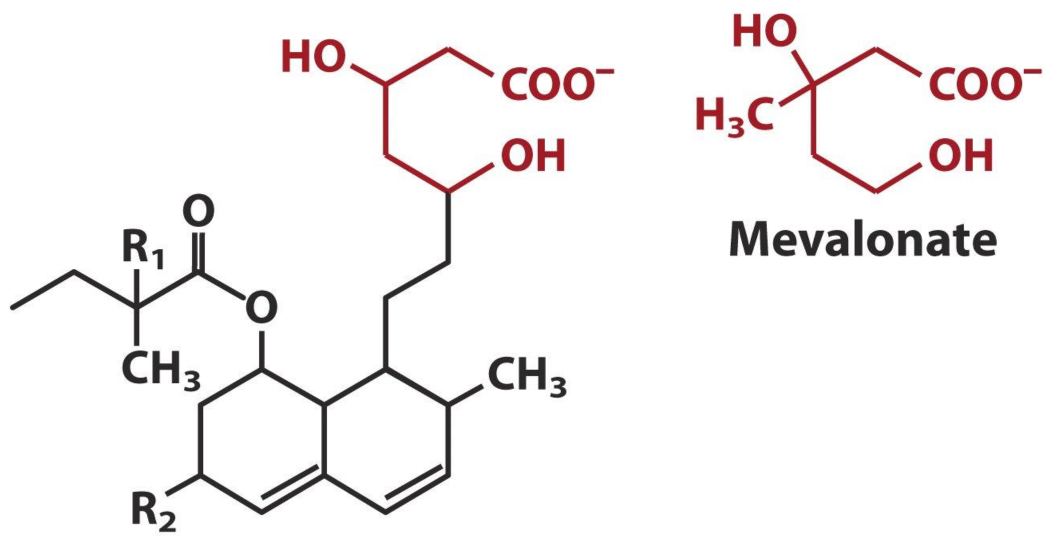
Natural & Pharmaceutical-based Regulation of Cholesterol / Sterol Production

● Cholesterol synthesis is an energy-expensive complex process in the cell. Thus it is heavily regulated.

● The major committed, rate-limiting step of sterol production is the formation of Mevalonate from β-Hydroxy-β-methyl-glutaryl-CoA by the enzyme **HMG-CoA reductase**.

● HMG-CoA reductase is, therefore, popular target of many drugs, called **statins**.

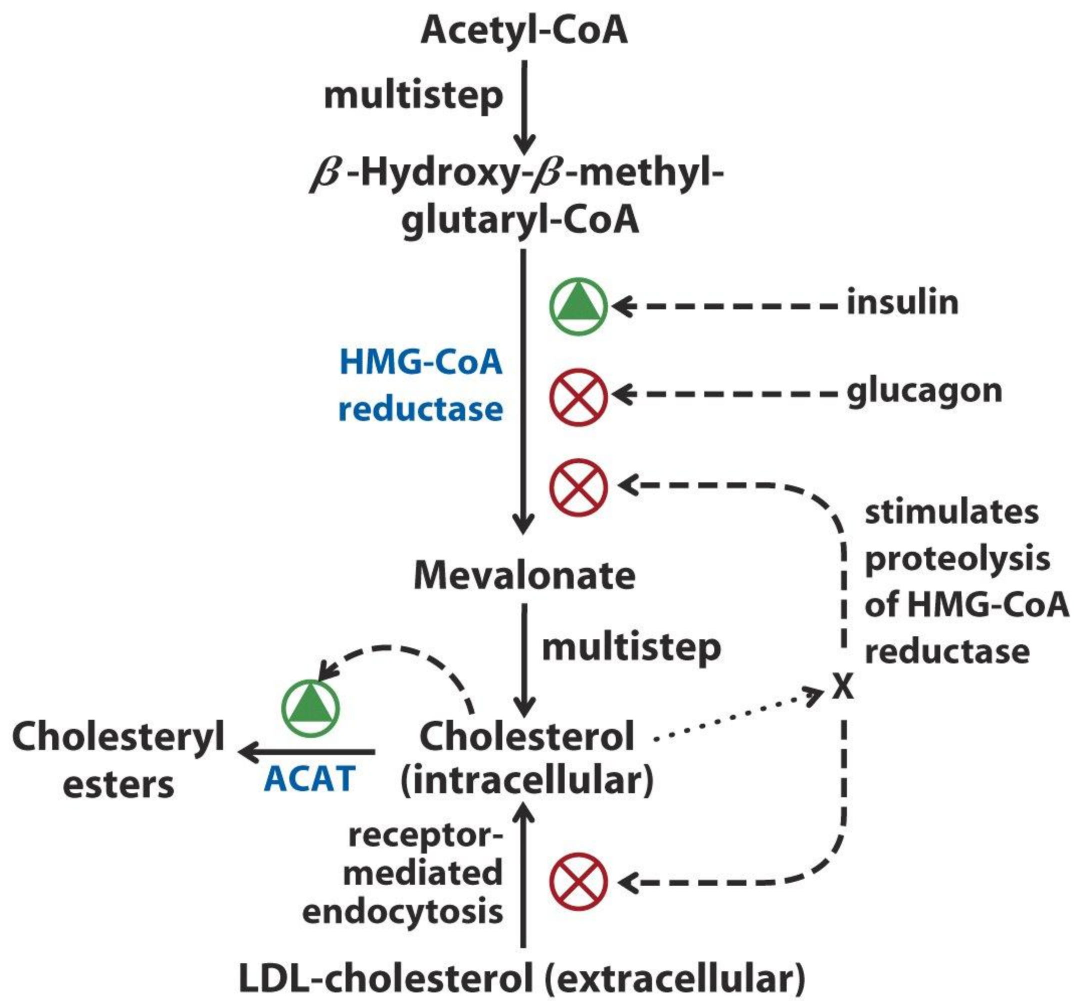
● Statins and all derivative of fungal natural products; they are blockbuster billion dollar a year drugs.



R_1 = H	R_2 = H	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
R_1 = H	R_2 = OH	Pravastatin (Pravachol)
R_1 = H	$R_2 = CH_3$	Lovastatin (Mevacor)

Natural Regulation of Choletserol Biosynthesis

- Transcriptional regulation.
- Hormonal regulatiuon: glucagon and insulin change activity of HMG-CoA reductase.
- Excess cholesterol stimulates proteolysis of HMG-CoA reductase.



END OF CLASS.

GOOD LUCK ON THE FINAL!