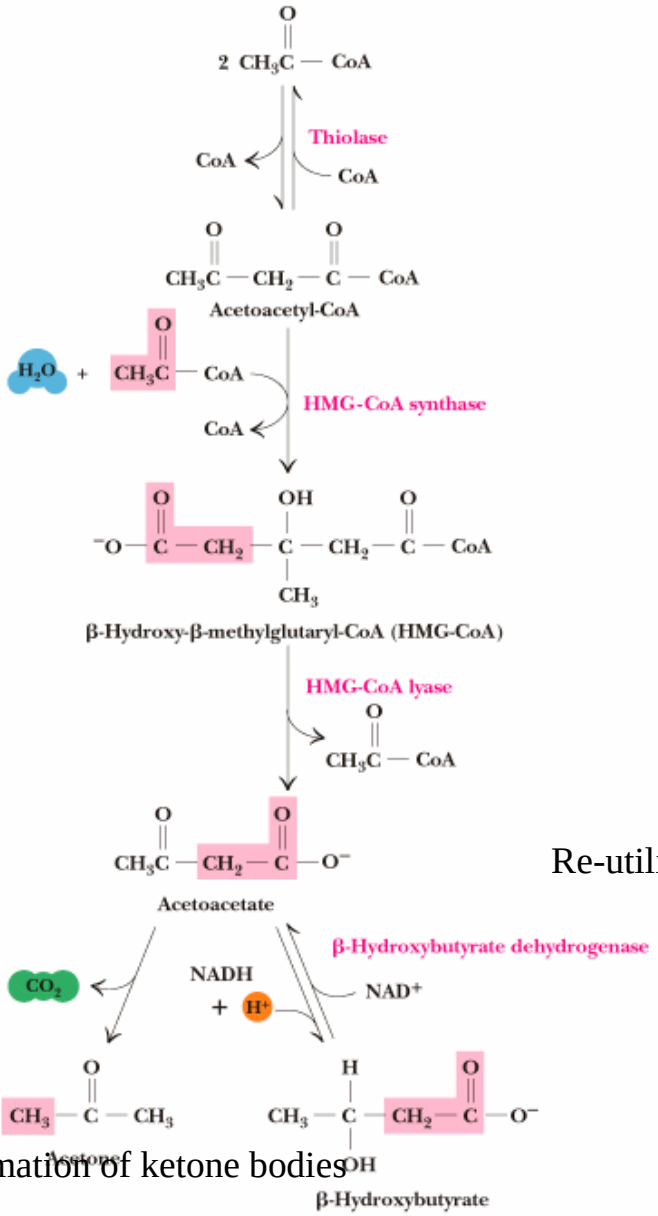
Biochemistry **Dr. Ayyed AlMossawi**

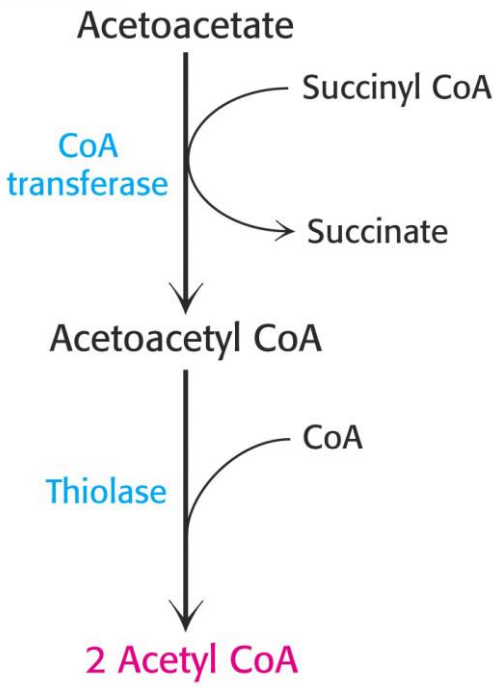
Lipid metabolism (Part 2)

Ketone Bodies

A special source of fuel and energy for certain tissues. Ketone bodies produced when acetyl-CoA levels exceed the capacity of the TCA cycle (depends on OAA levels). Under starvation, some of the acetyl-CoA produced by fatty acid oxidation in liver mitochondria is converted to acetone, acetoacetate and β-hydroxybutyrate. These are called "ketone bodies" Source of fuel for brain, heart and muscle. Ketone bodies are Major energy source for brain during starvation. They are also represent transportable forms of fatty acid



Formation of ketone bodies



Re-utilization of ketone bodies

Ketone Bodies and Diabetes

Lack of insulin related to uncontrolled fat breakdown in adipose tissues leading to excess beta-oxidation of fatty acids results in ketone body formation.so we can often smell acetone on the breath of diabetics. High levels of ketone bodies leads to condition known as diabetic ketoacidosis, accumulation ketone bodies can lower blood pH because ketone bodies are acids

Fatty Acid Biosynthesis

Synthesis takes place in the cytosol. Intermediates covalently linked to acyl carrier protein. Activation of each acetyl CoA.

acetyl CoA + CO_2 $\longrightarrow$ Malonyl CoA

Four-step repeating cycle, extension by 2-carbons /cycle

– Condensation

– Reduction

– Dehydration

– reduction

The enzymes of fatty acid synthesis are packaged together in a complex called as fatty acid synthase (FAS).

• The product of FAS action is palmitic acid. (16:0).

Citrate Shuttle

• FAs are synthesized in the cytoplasm from acetylCoA

• Acetyl CoA generated from pyruvate by the action of PDH and by β-oxidation of fatty acids is in the mitochondria.

• For fatty acid biosynthesis, acetyl CoA has to be transported from the mitochondria to the cytoplasm. This is done via a shuttle system called the **Citrate Shuttle**.

• Acetyl CoA reacts with oxaloacetate to give citrate. A **tricarboxylate translocase** transports citrate from mitochondria to cytosol.

• In the cytosol, citrate is cleaved back to oxaloacetate and acetylCoA. This reaction is catalyzed by ATP-citrate lyase and requires the hydrolysis of one molecule of ATP

Oxaloacetate is converted back to pyruvate for re-entry into mitochondria

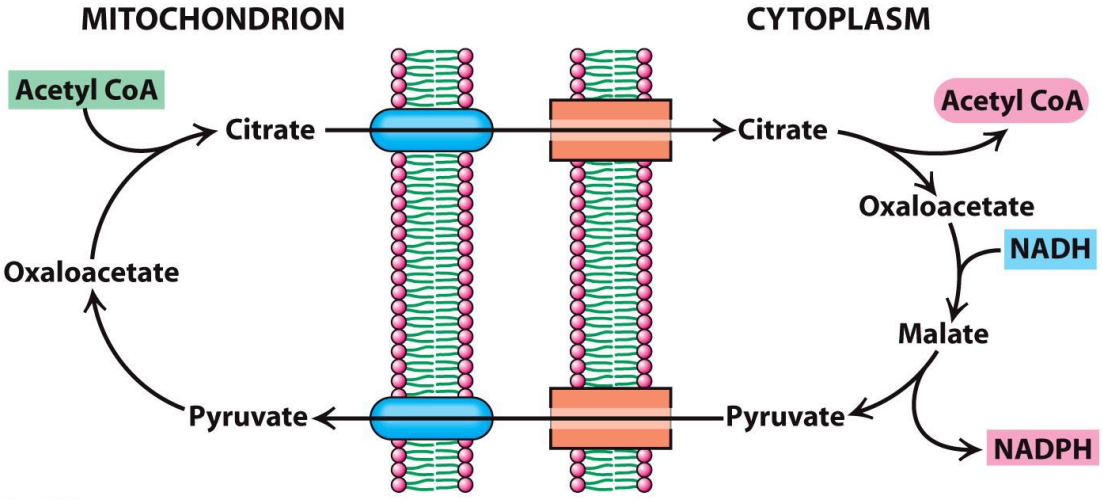


Figure 28.1
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Malonyl-CoA formation

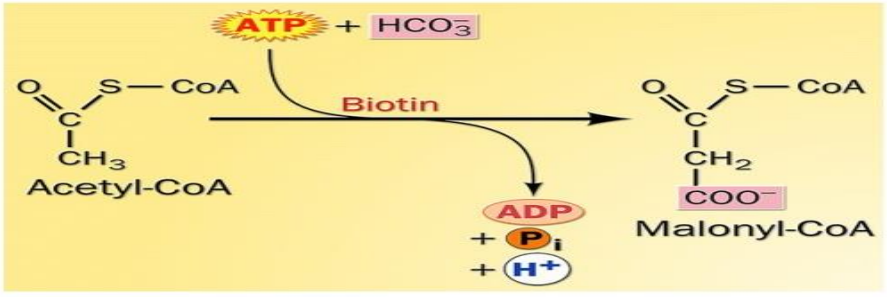
The input to fatty acid synthesis is acetyl-CoA, which is carboxylated to malonyl-CoA. ATP-dependent carboxylation provides energy input.

The CO2 is lost later during condensation with the growing fatty acid.

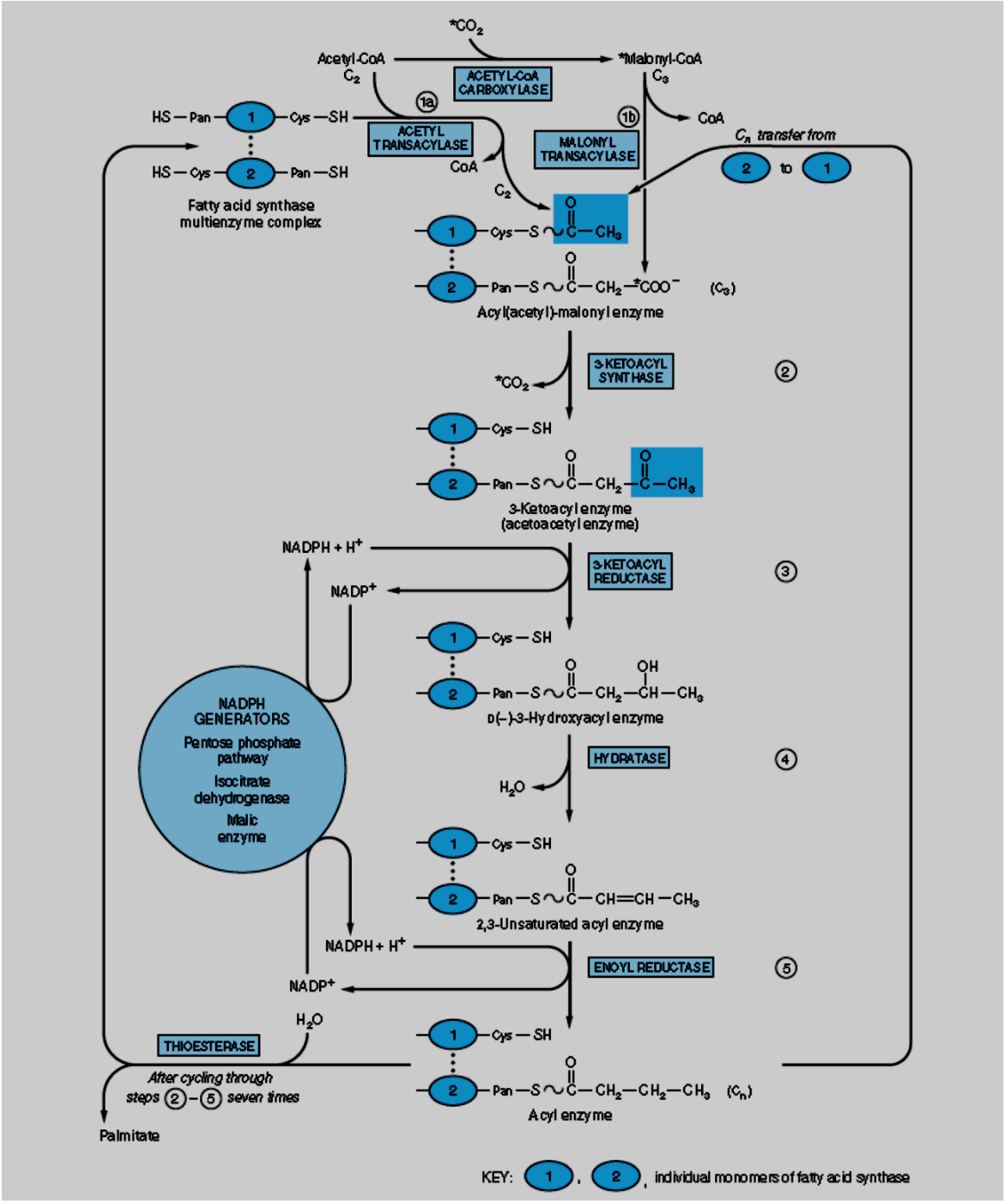
Malonyl CoA is synthesized by the action of acetyl-CoA carboxylase. Biotin is a required cofactor.

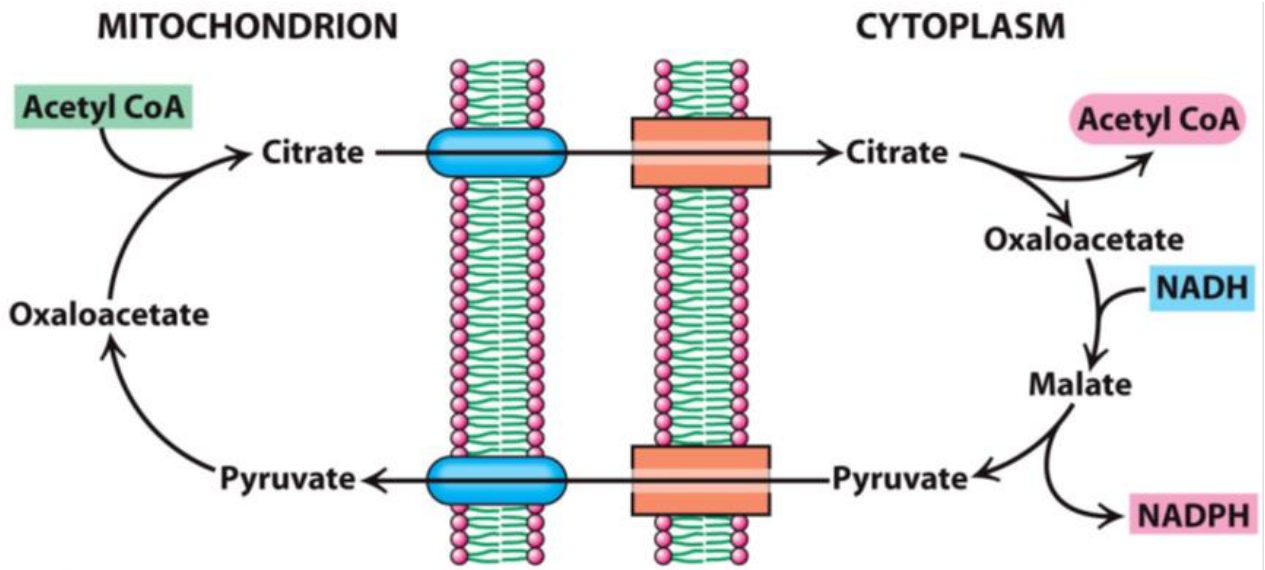
• This is an irreversible reaction. AcetylCoA carboxylation is a rate-limiting step of FA biosynthesis.

• Acetyl-CoA carboxylase is under allosteric regulation. Citrate is a positive effector and palmitoyl- CoA is a negative effector.



Activation of acetate : Acetyl-CoA to malonyl CoA


*CO2
Acetyl-CoA
C2
*Malonyl-CoA
C3
ACETYL-CoA CARBOXYLASE
1a
1b
CoA
HS — Pan — 1 — Cys — SH
HS — Cys — 2 — Pan — SH
ACETYL TRANSACYLASE
MALONYL TRANSACYLASE
Cn transfer from 2 to 1
Fatty acid synthase multienzyme complex
Acyl(acetyl)-malonyl enzyme
(C3)
*CO2
3-KETOACYL SYNTHASE
2
3-Ketoacyl enzyme (acetoacetyl enzyme)
NADPH + H+
NADP+
3-KETOACYL REDUCTASE
3
D(–)-3-Hydroxyacyl enzyme
NADPH GENERATORS
Pentose phosphate pathway
Isocitrate dehydrogenase
Malic enzyme
H2O
HYDRATASE
4
2,3-Unsaturated acyl enzyme
NADPH + H+
NADP+
ENOYL REDUCTASE
5
H2O
THIOESTERASE
After cycling through steps 2–5 seven times
Acyl enzyme
(Cn)
Palmitate
KEY: 1, 2, individual monomers of fatty acid synthase



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