Chem 352 - Lecture 10
Lipid, Amino Acid, and Nucleotide Metabolism
Part I: Lipid Metabolism

Introduction

In Lecture 10 we will add some of the peripheral pathways in metabolism that lead to synthesis and degradation three important classes of biomolecules:

- Lipids
- Amino acids
- Nucleotides

Introduction

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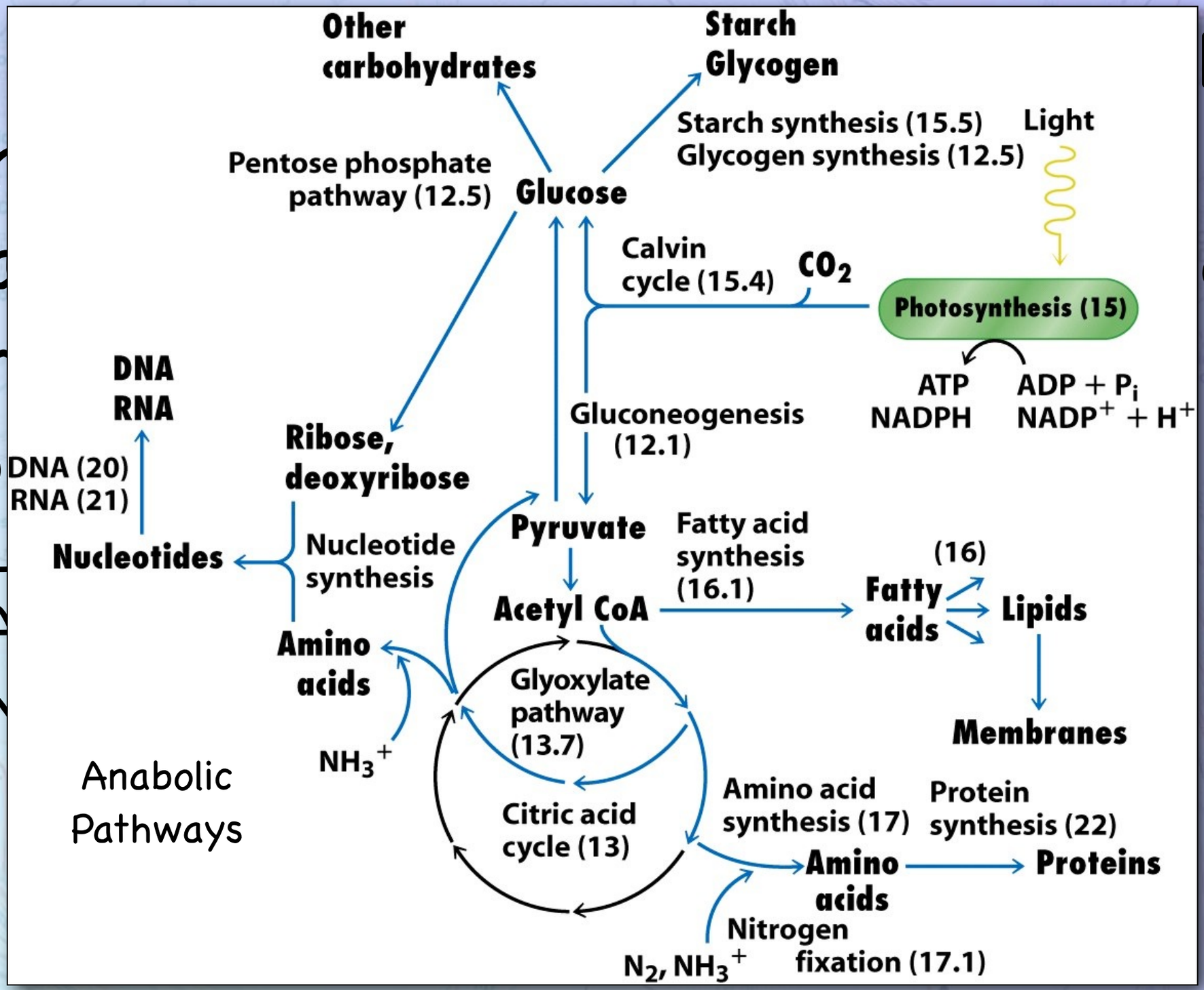

Anabolic Pathways

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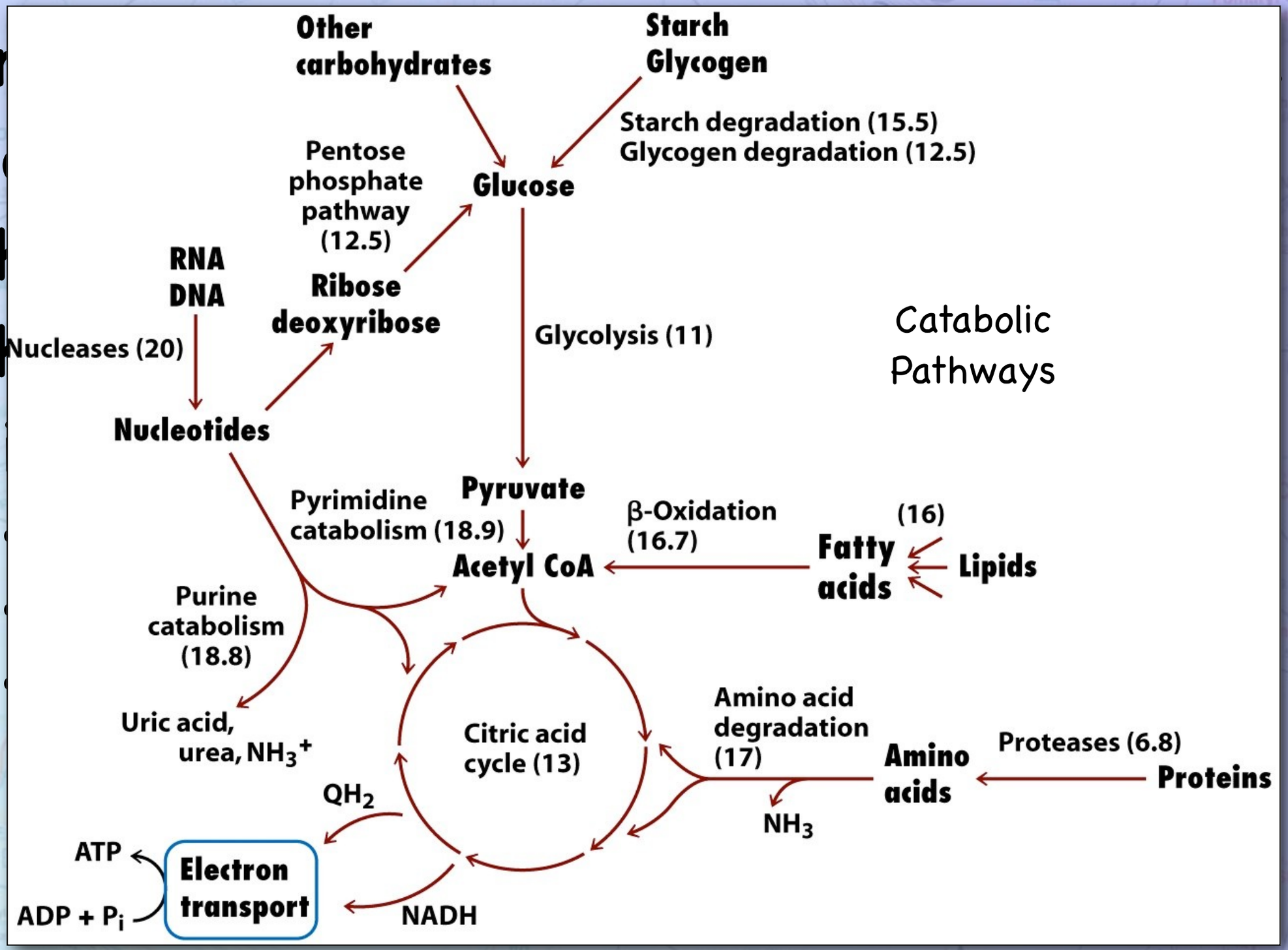

Catabolic Pathways

Introduction

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Introduction

Lipids play many important cellular roles

- Membrane components (phospholipids, et al. and cholesterol)
- Fuels (Triacylglycerides)
  - Meet long term energy needs in mammals
- Regulators (steroids, eicosanoids)

We will focus on just a couple of key metabolic pathways.

Introduction

We will focus on the following sections from Chapter 16

- 16.1: Fatty Acid Synthesis
- 16.6: Synthesis of Cholesterol
- 16.7: Fatty Acid Oxidation
- 16.9: Lipid Metabolism is Regulated by Hormones in Mammals
- 16.10: Absorption and Mobilization of Fuel Lipids in Mammals
- 16.11: Ketone Bodies Are Fuel Molecules

Fatty Acid Synthesis

Fatty acids are synthesized by the repetitive addition of 2 carbon units to a growing chain.

- Acetyl-CoA is the source of the 2 carbon units.
- The Acetyl groups are activated by carboxylating them to Malonyl groups

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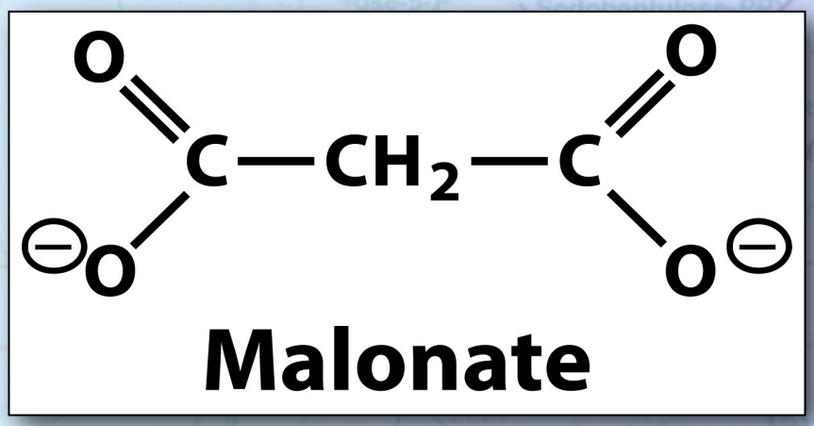

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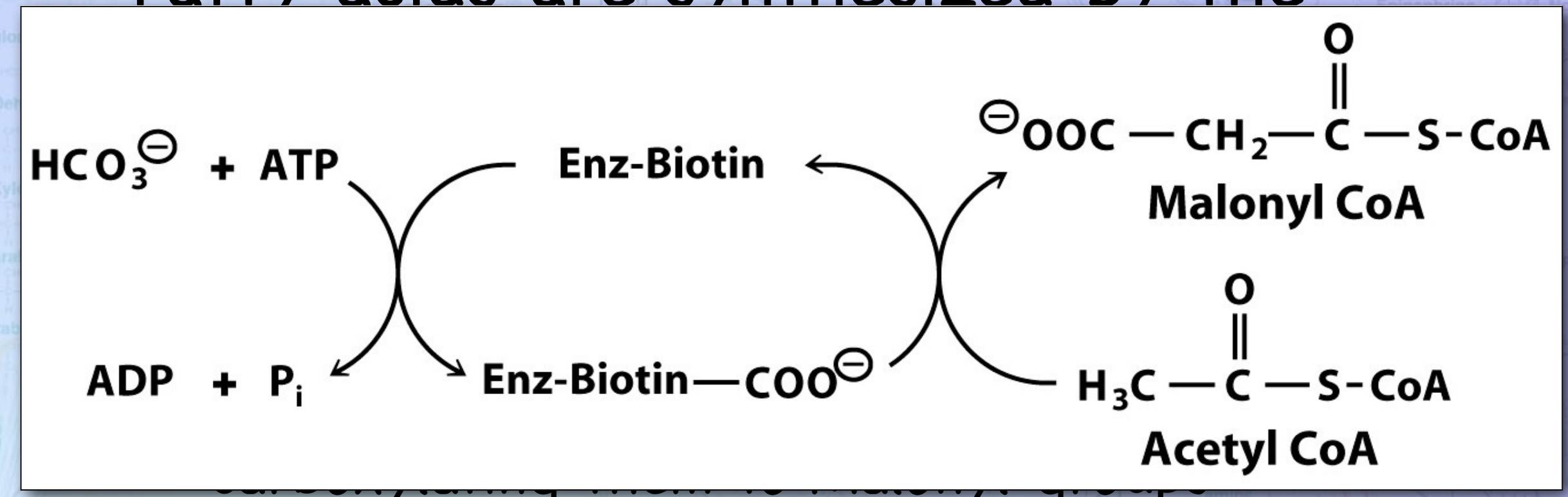

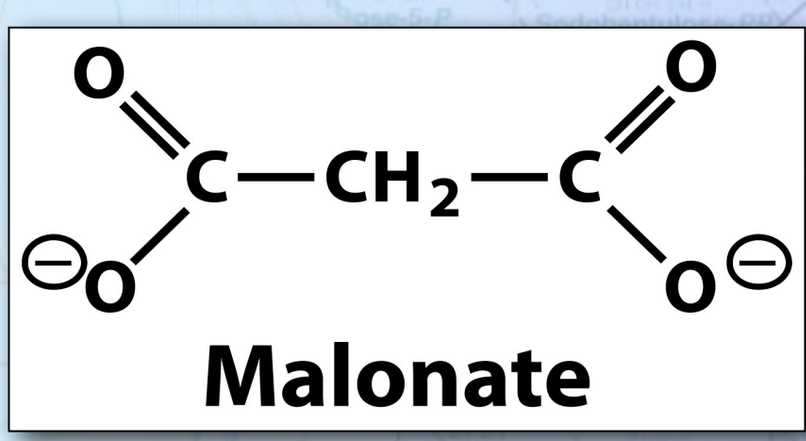

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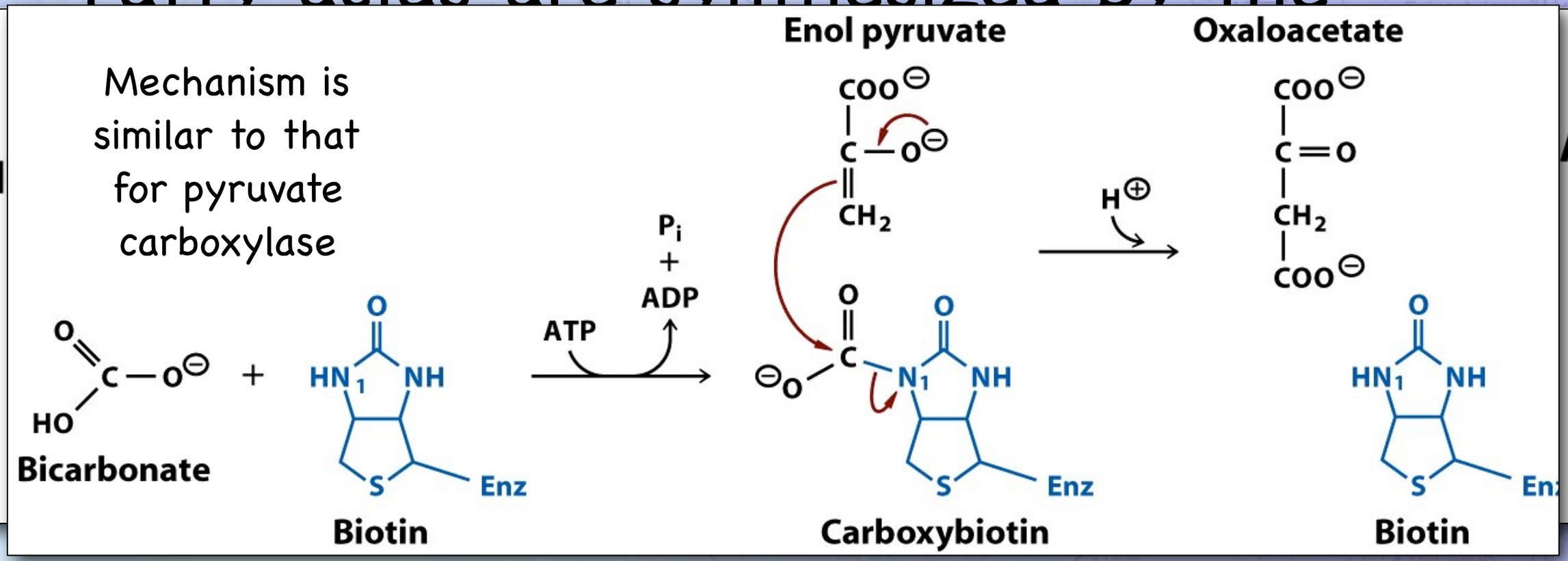
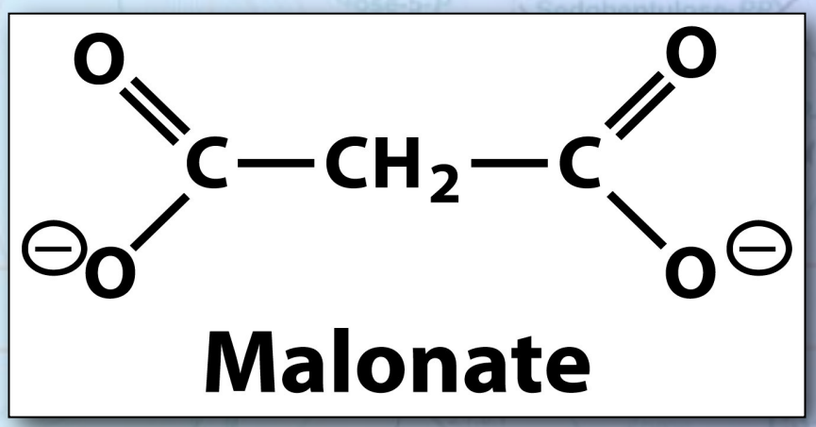
Mechanism is similar to that for pyruvate carboxylase





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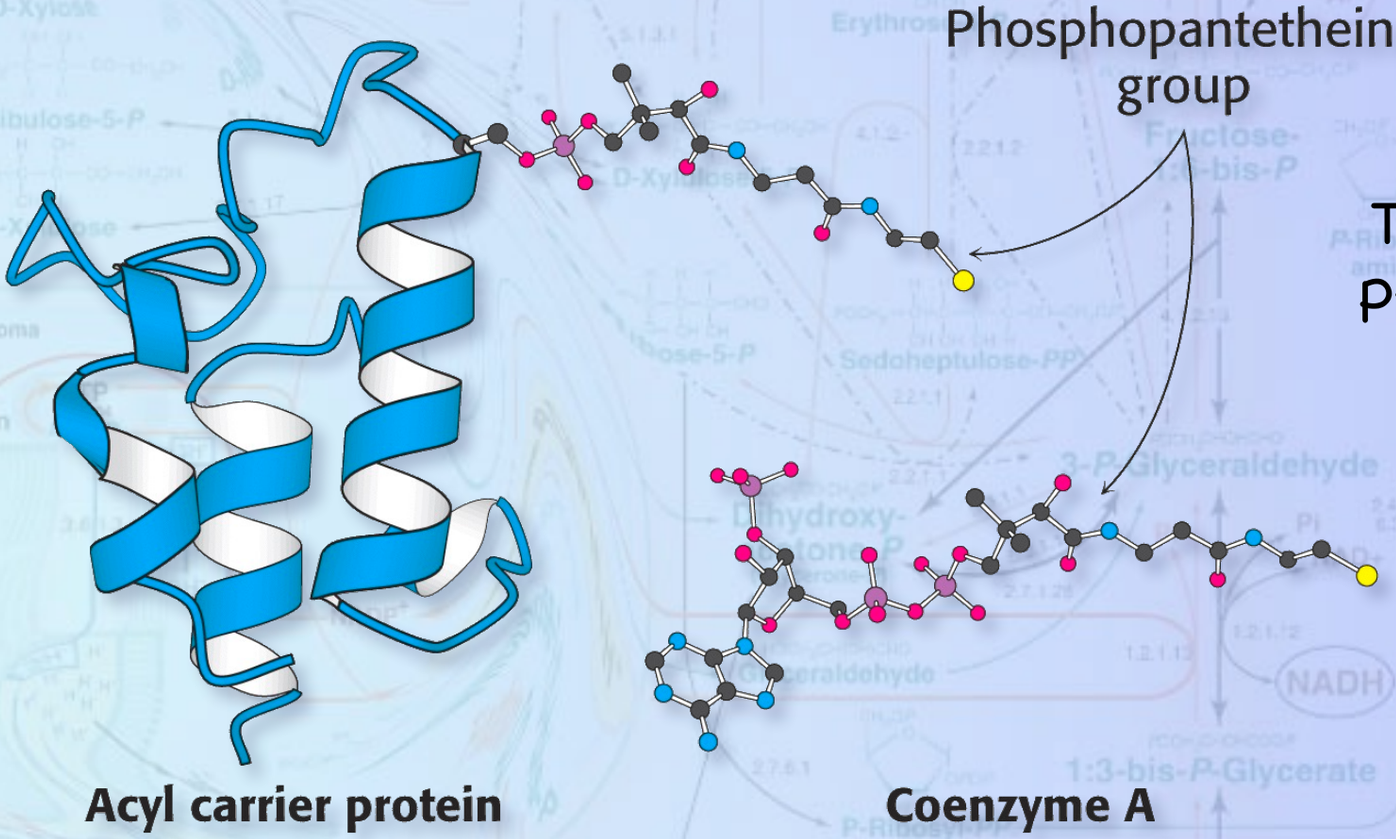
Fatty Acid Synthesis

In eukaryotes, both the growing chain, the acetyl group, and the malonyl group are attached to an acyl carrier protein (ACP)



The Acyl Carrier Protein resembles CoA-SH

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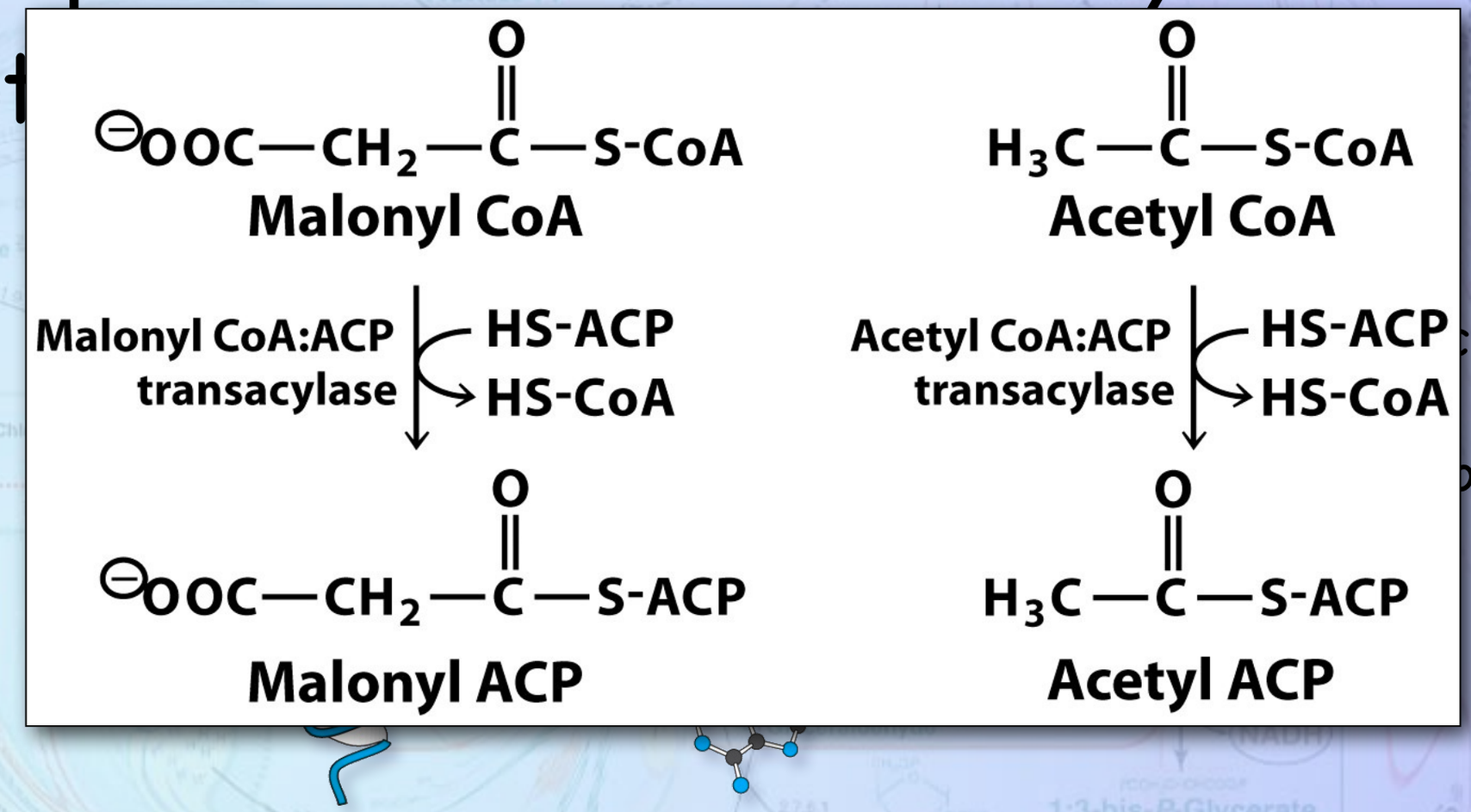

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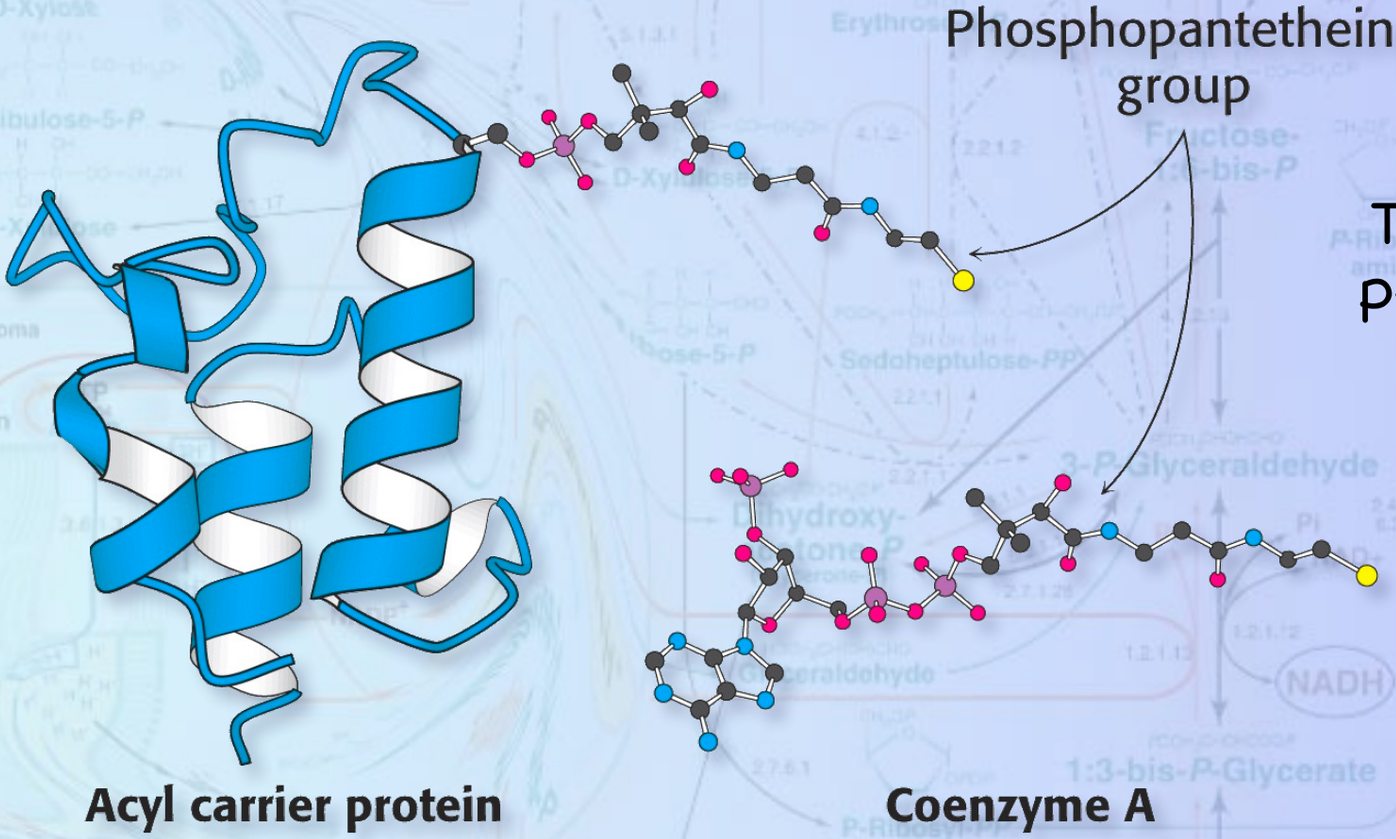

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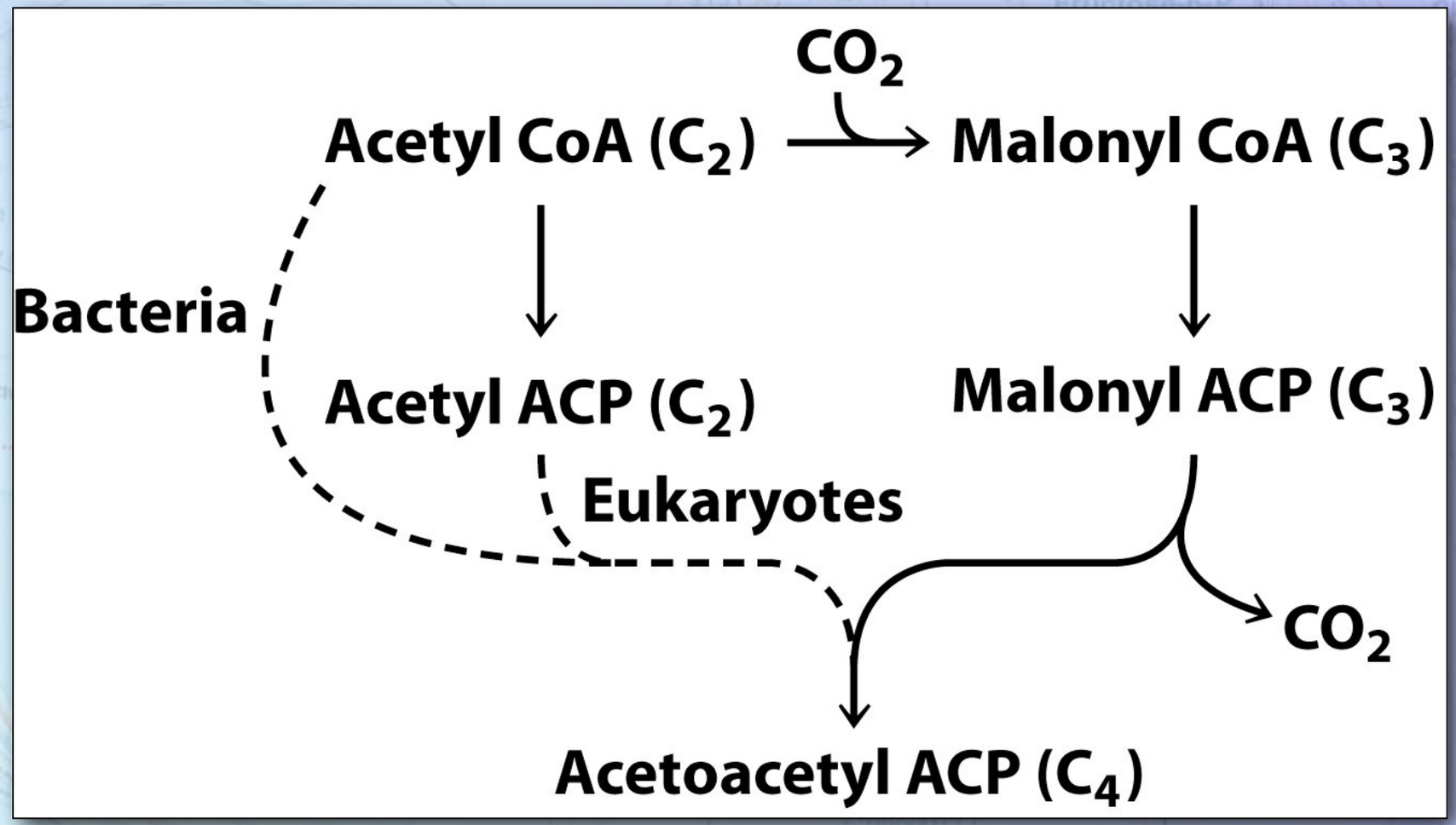
The ligation of an acetyl group to the growing chain is coupled to the decarboxylation of the malonyl group.



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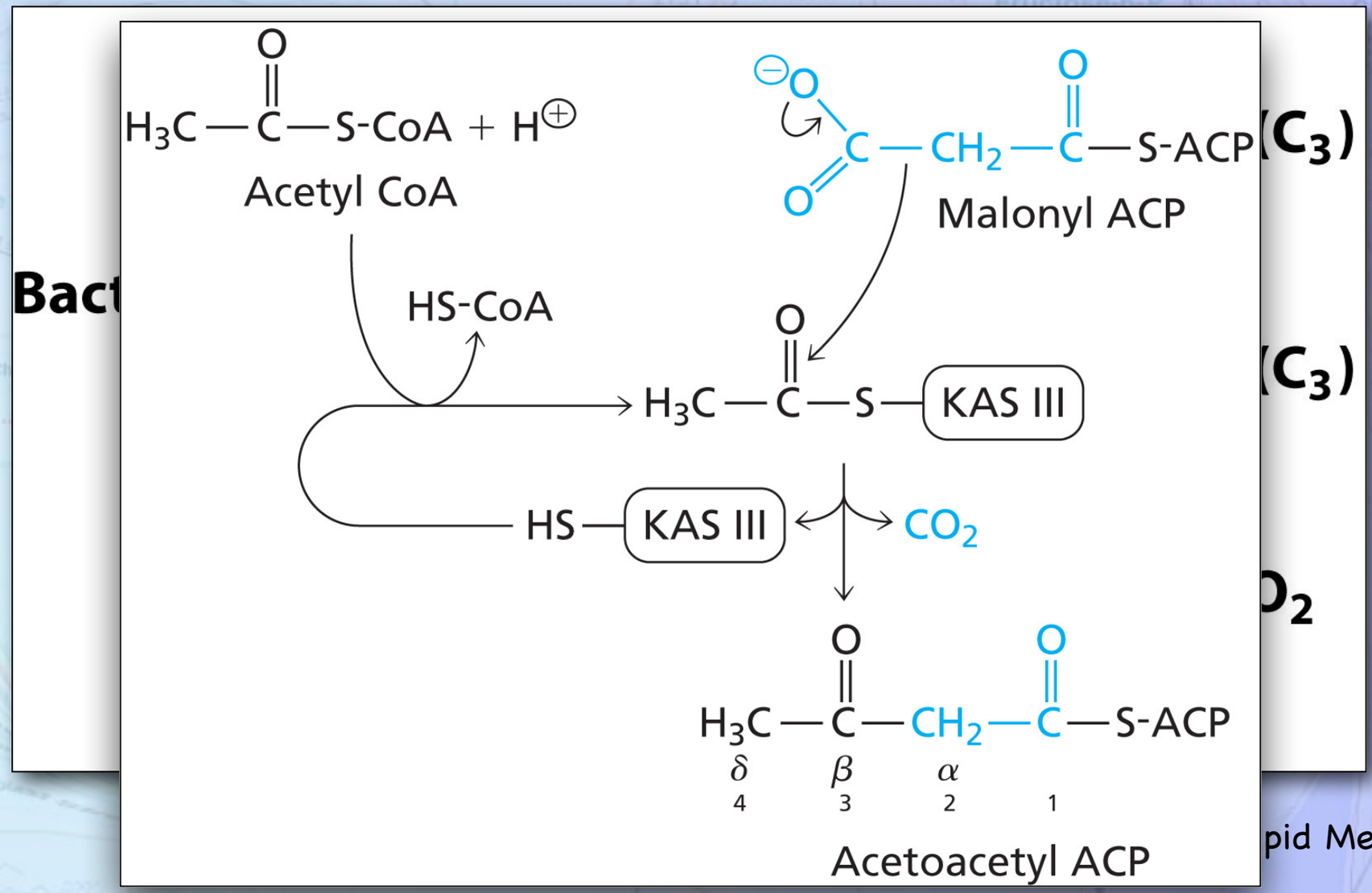

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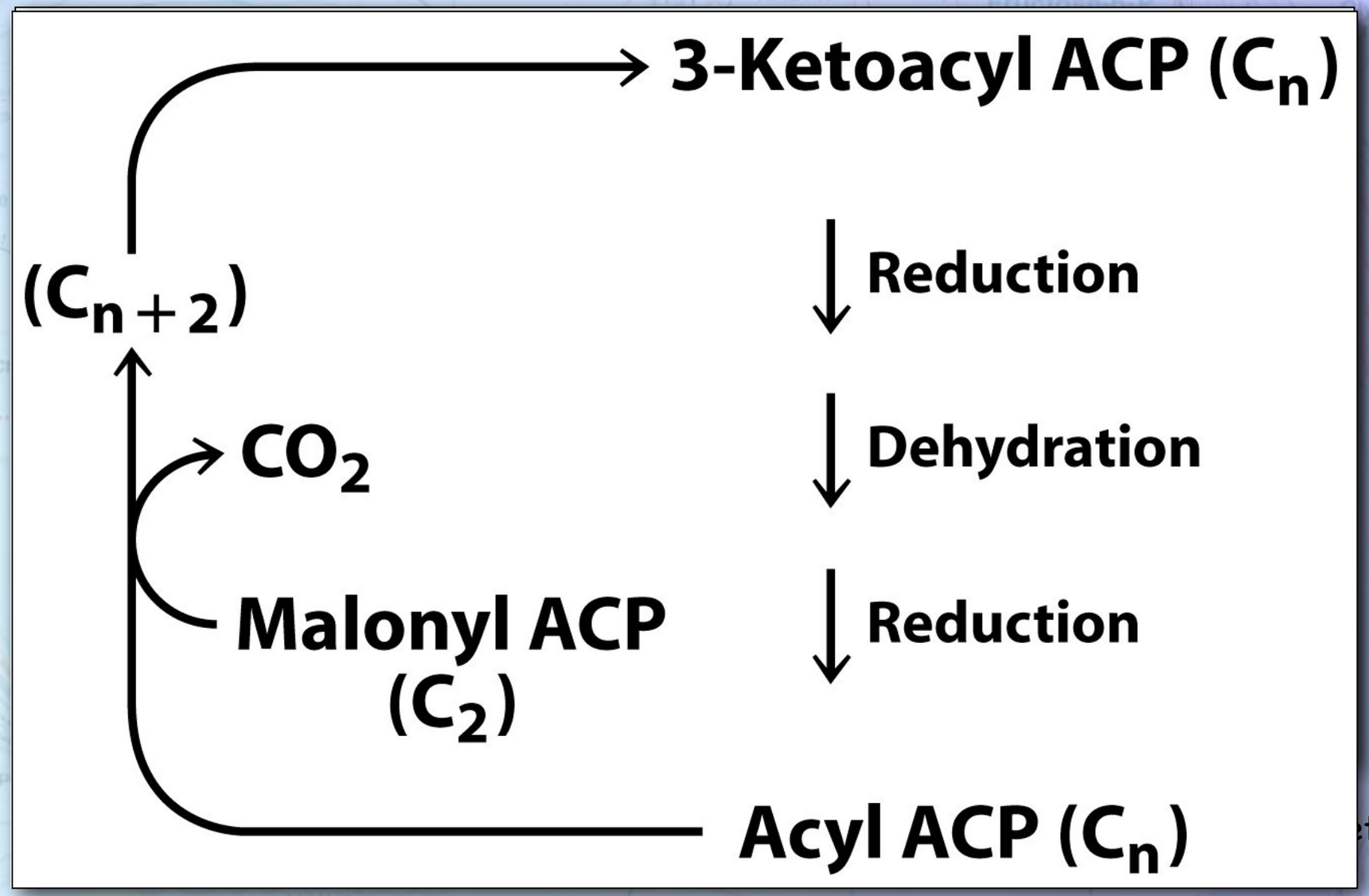
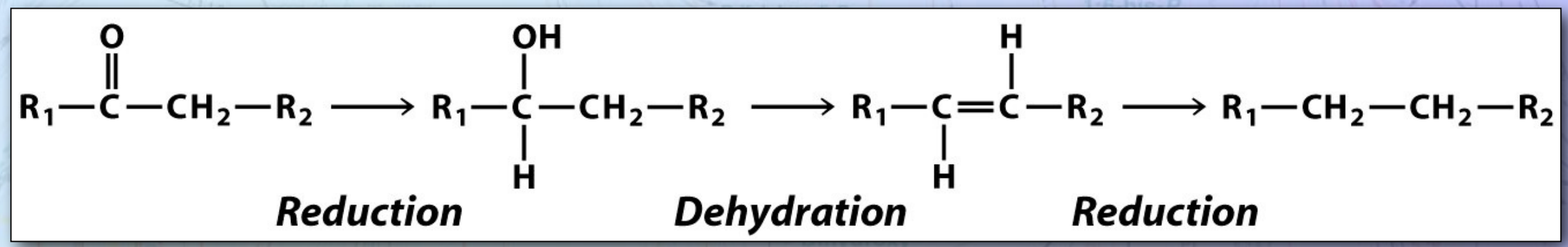


Fatty Acid Synthesis

The reduction/dehydration/reduction steps similar to a series of reactions found in the citric acid cycle, but in reverse order.



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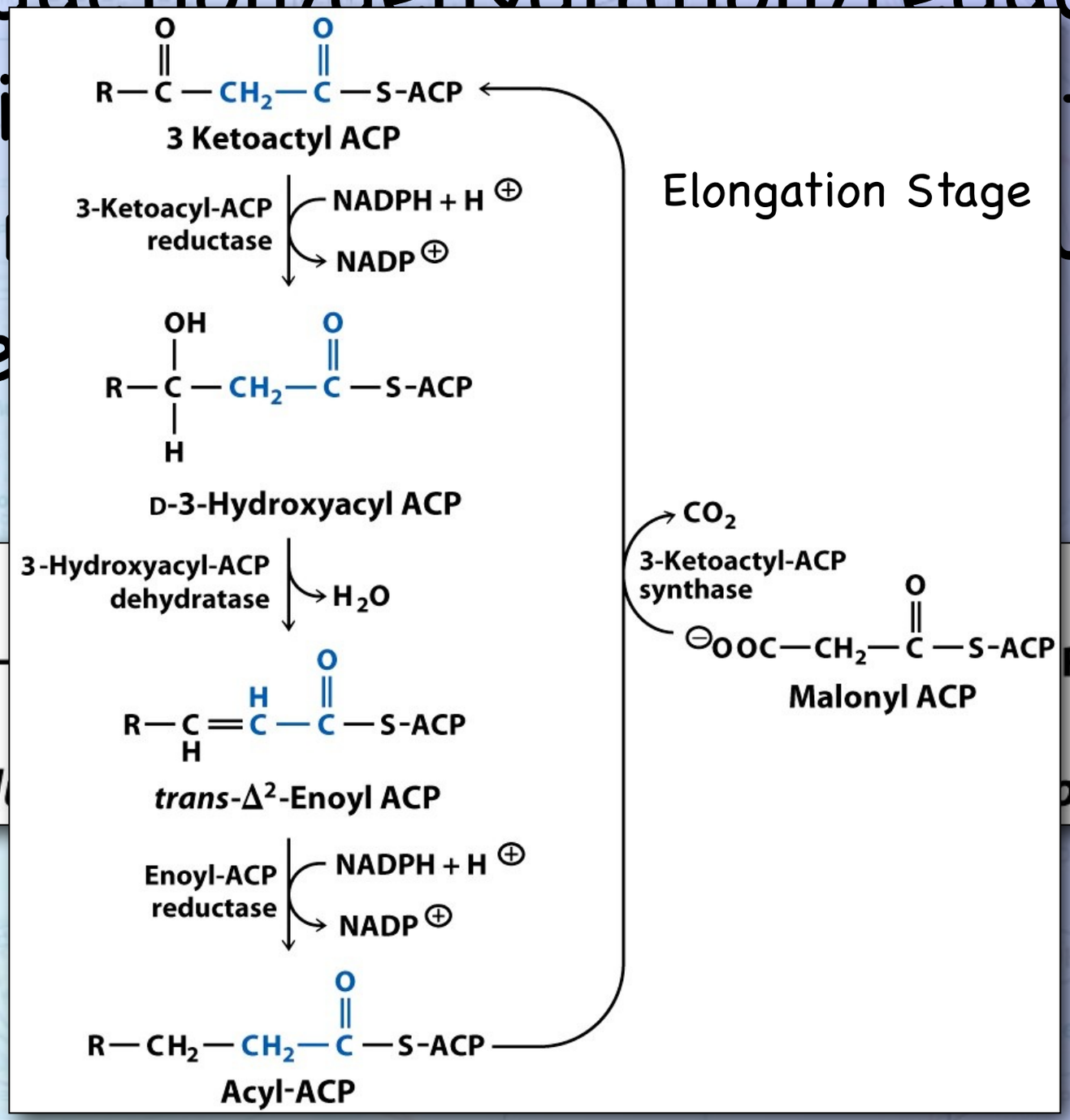

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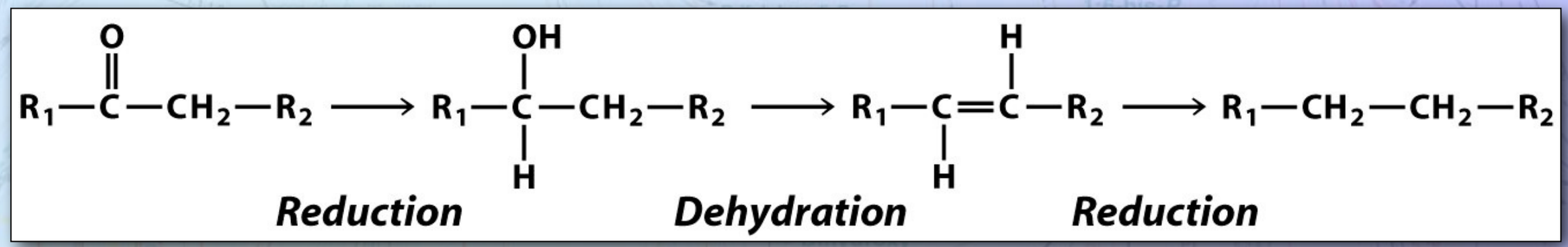
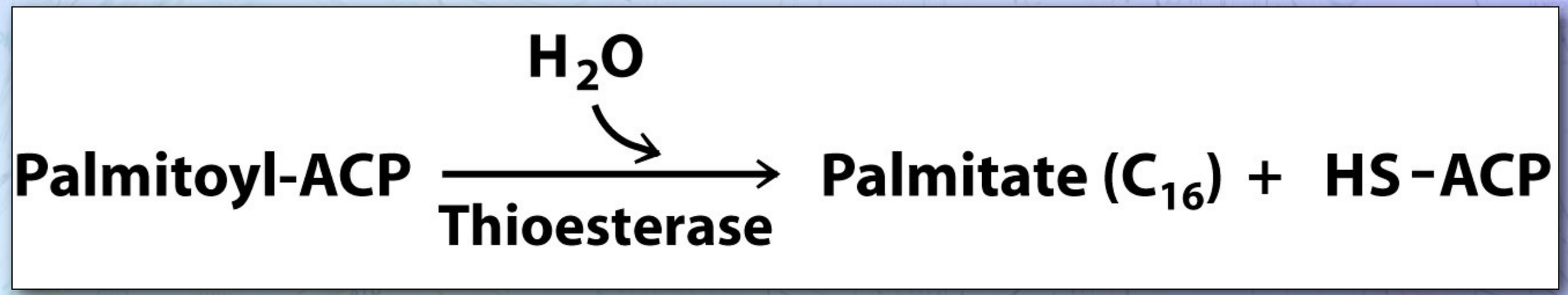


Fatty Acid Synthesis

The elongation continues until reaching 16 carbons (palmitic acid).

- The palmitoyl group is cleaved from the ACP by a thioesterase.



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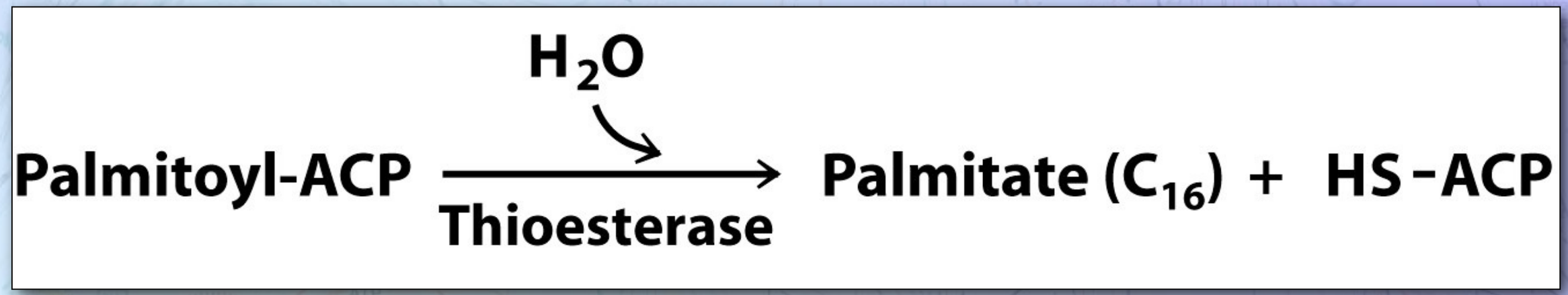

$$\text{Acetyl CoA} + 7\ \text{Malonyl CoA} + 14\ \text{NADPH} + 14\ H^{\oplus} \longrightarrow$$

$$\text{Palmitate} + 7\ CO_2 + 14\ NADP^{\oplus} + 8\ \text{HS–CoA} + 6\ H_2O$$

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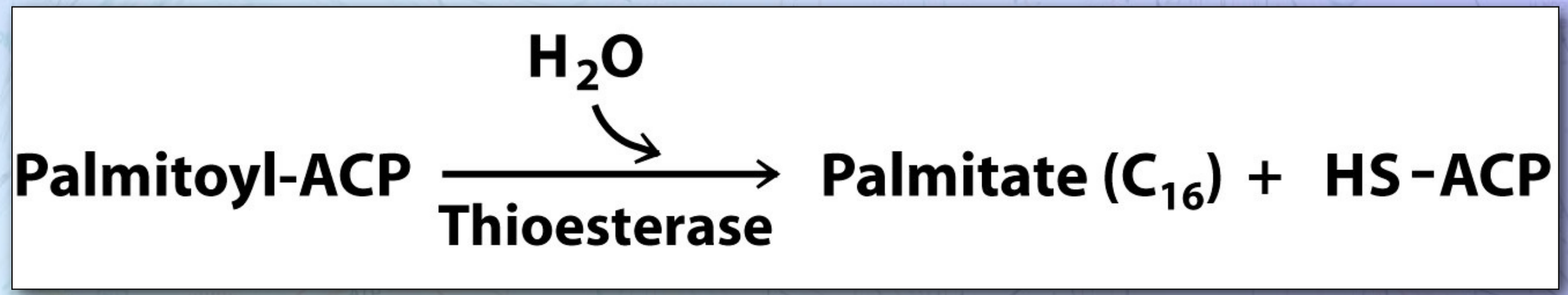
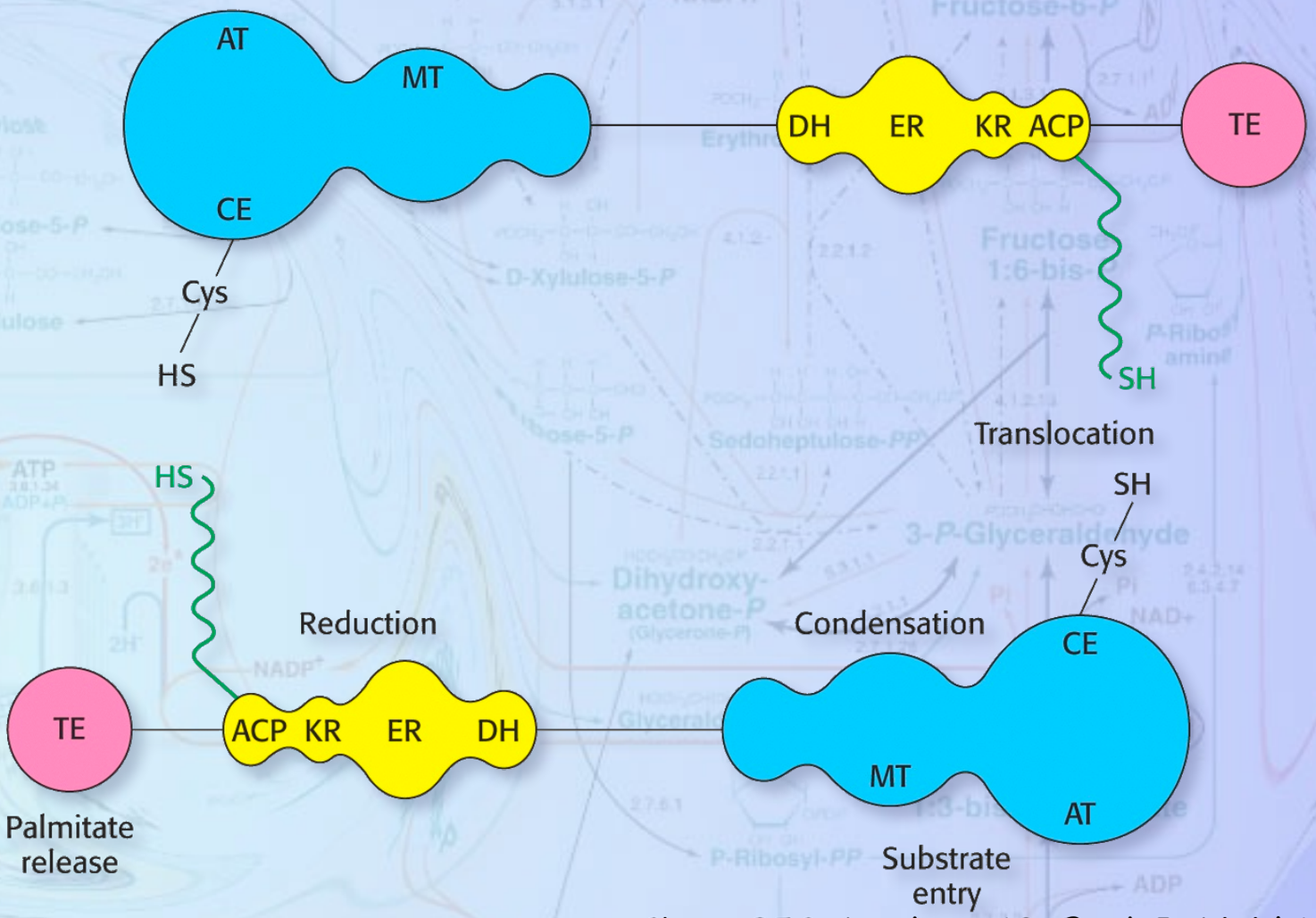


Fatty Acid Synthesis

In eukaryotes, all of the active sites for fatty acid synthesis are located on a single polypeptide.



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MT - malonyl transferase
CE - condensing enzyme
DH - dehydratase
ER - enoyl reductase
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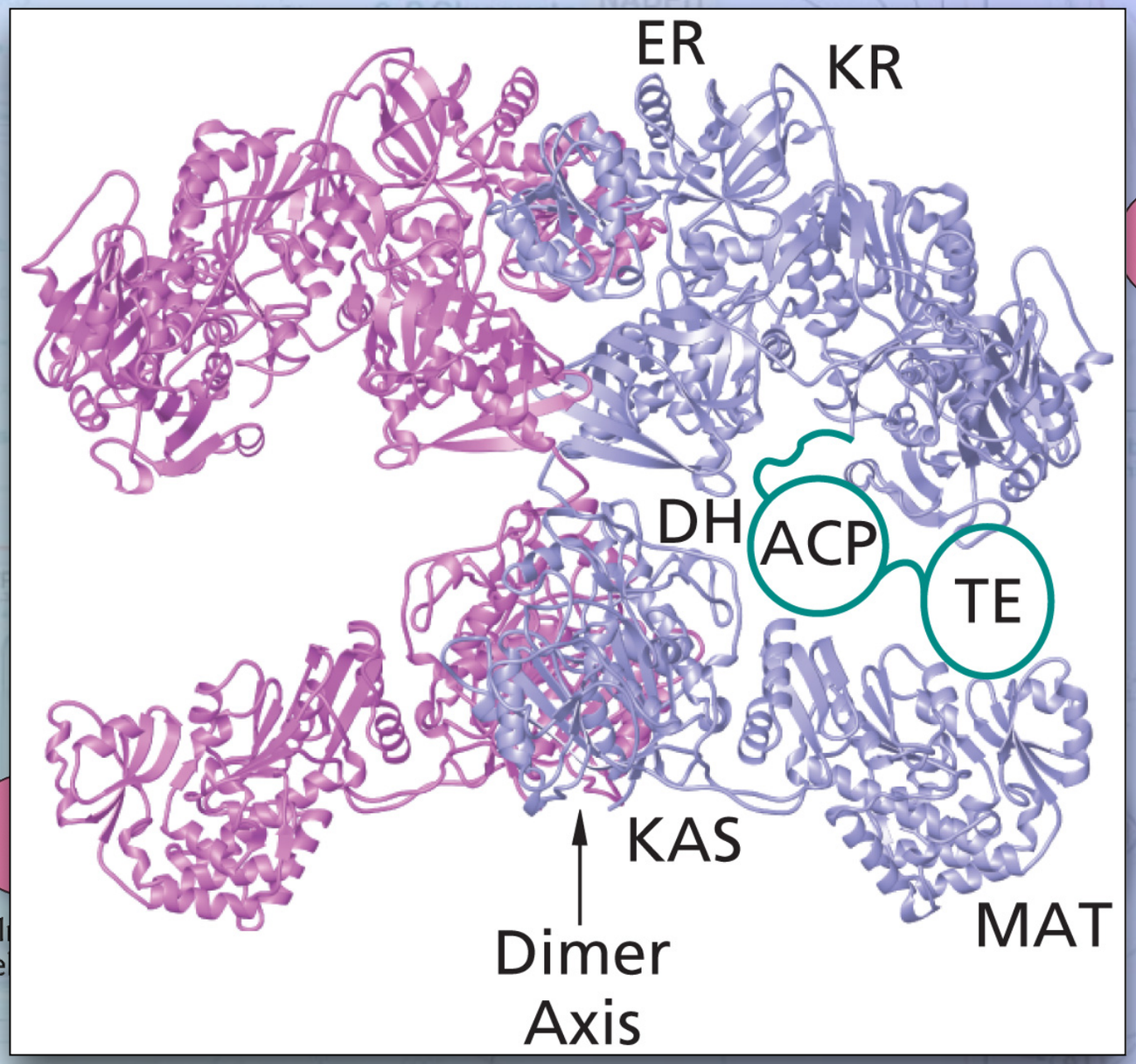

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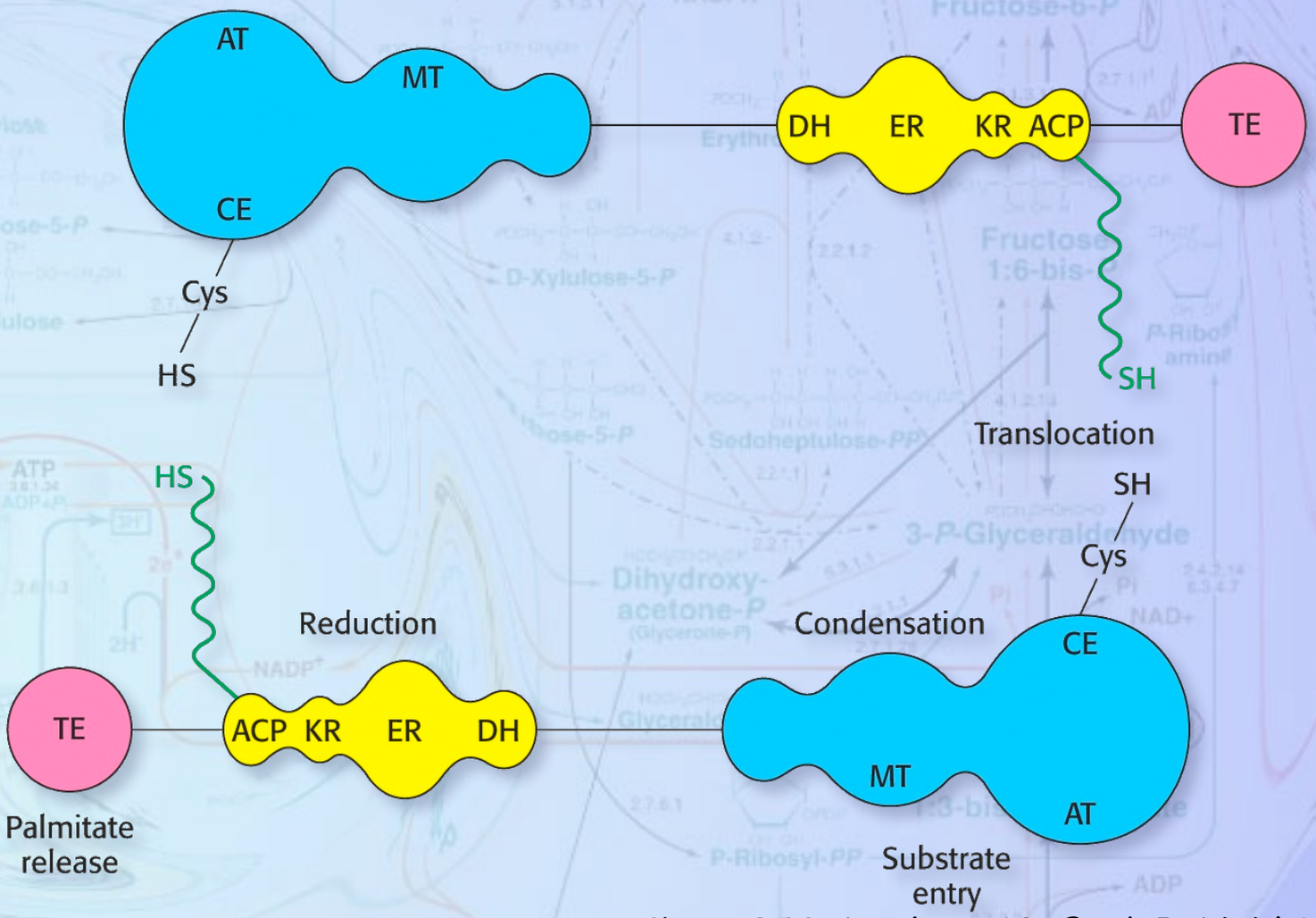

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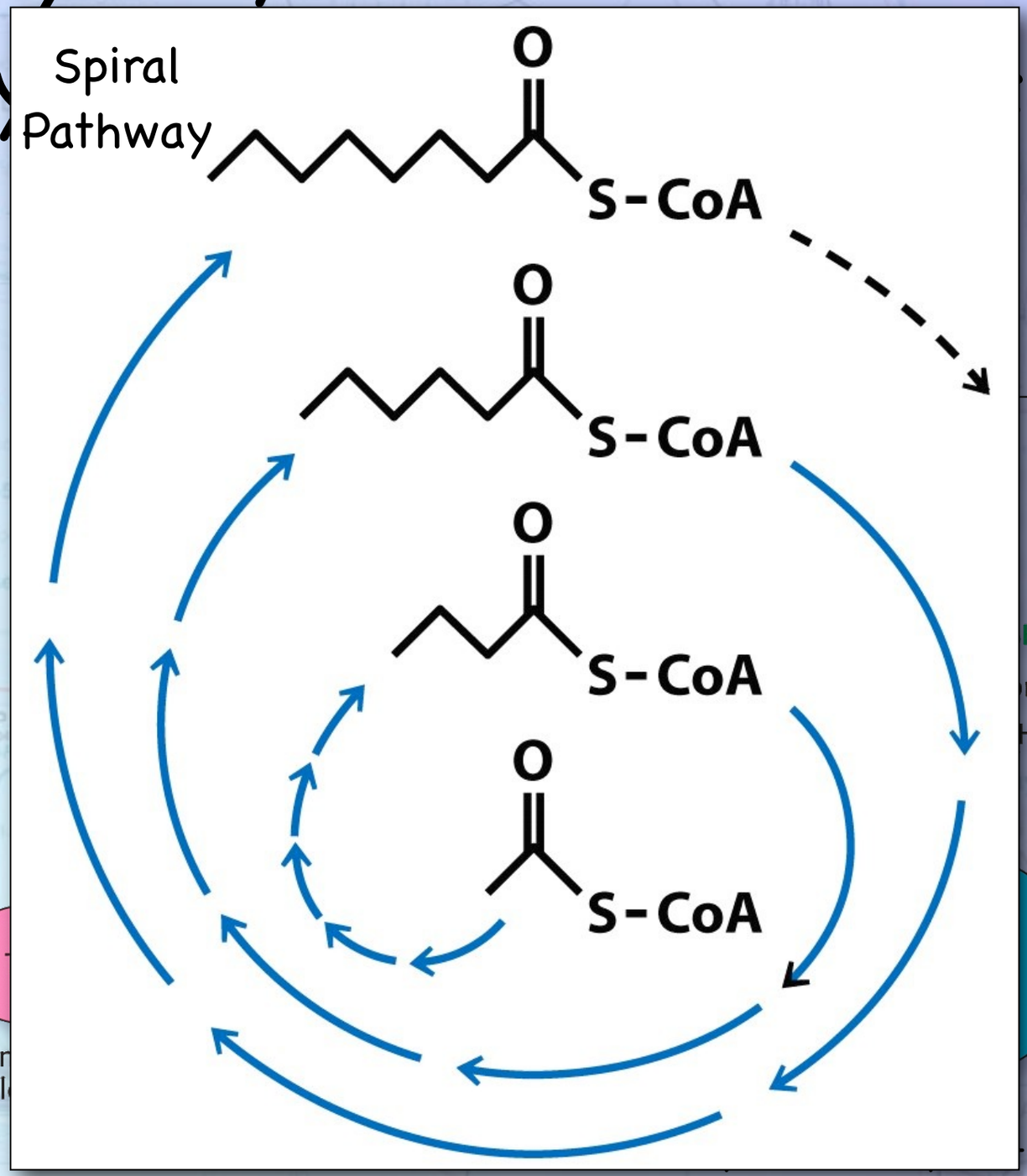

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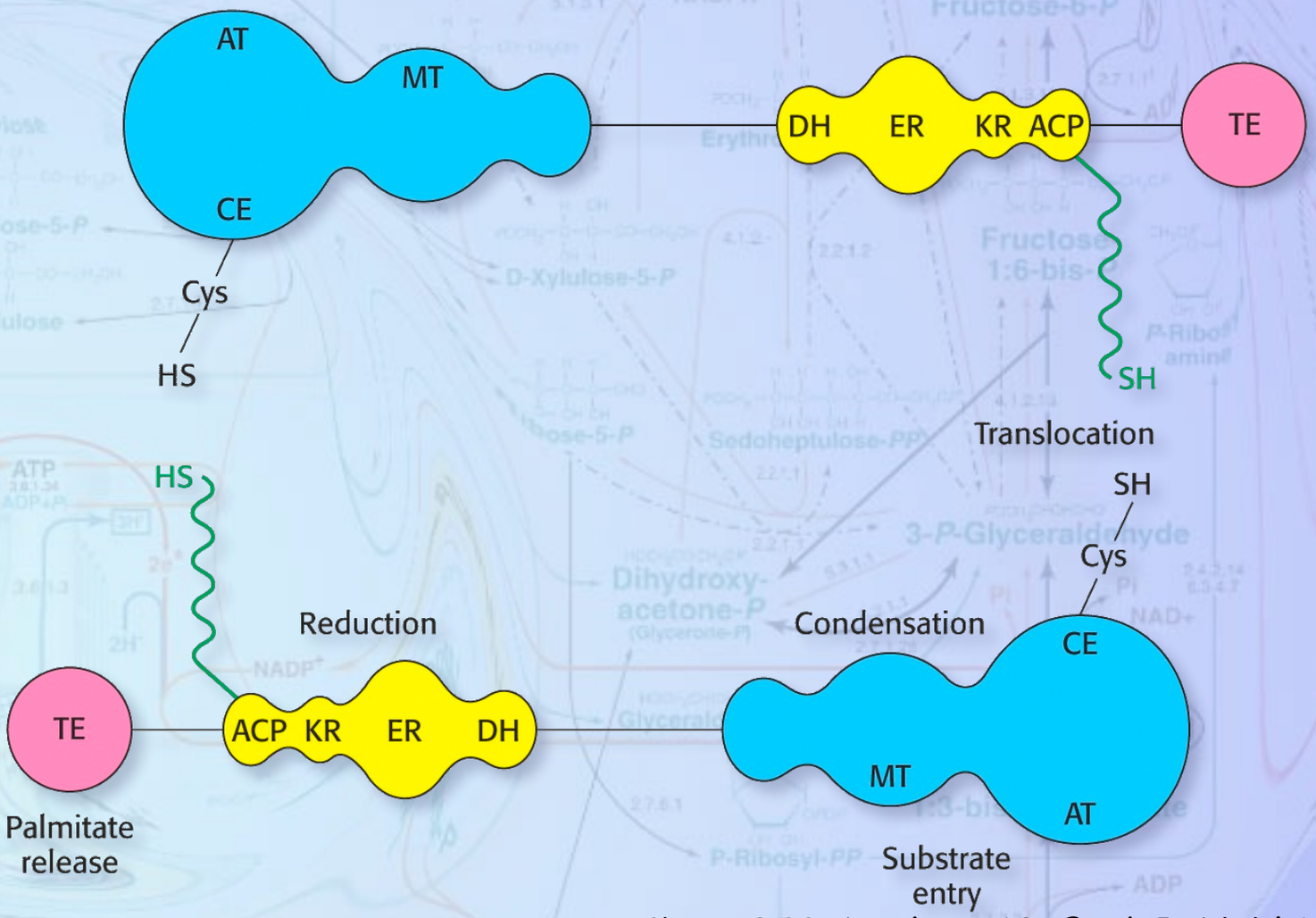

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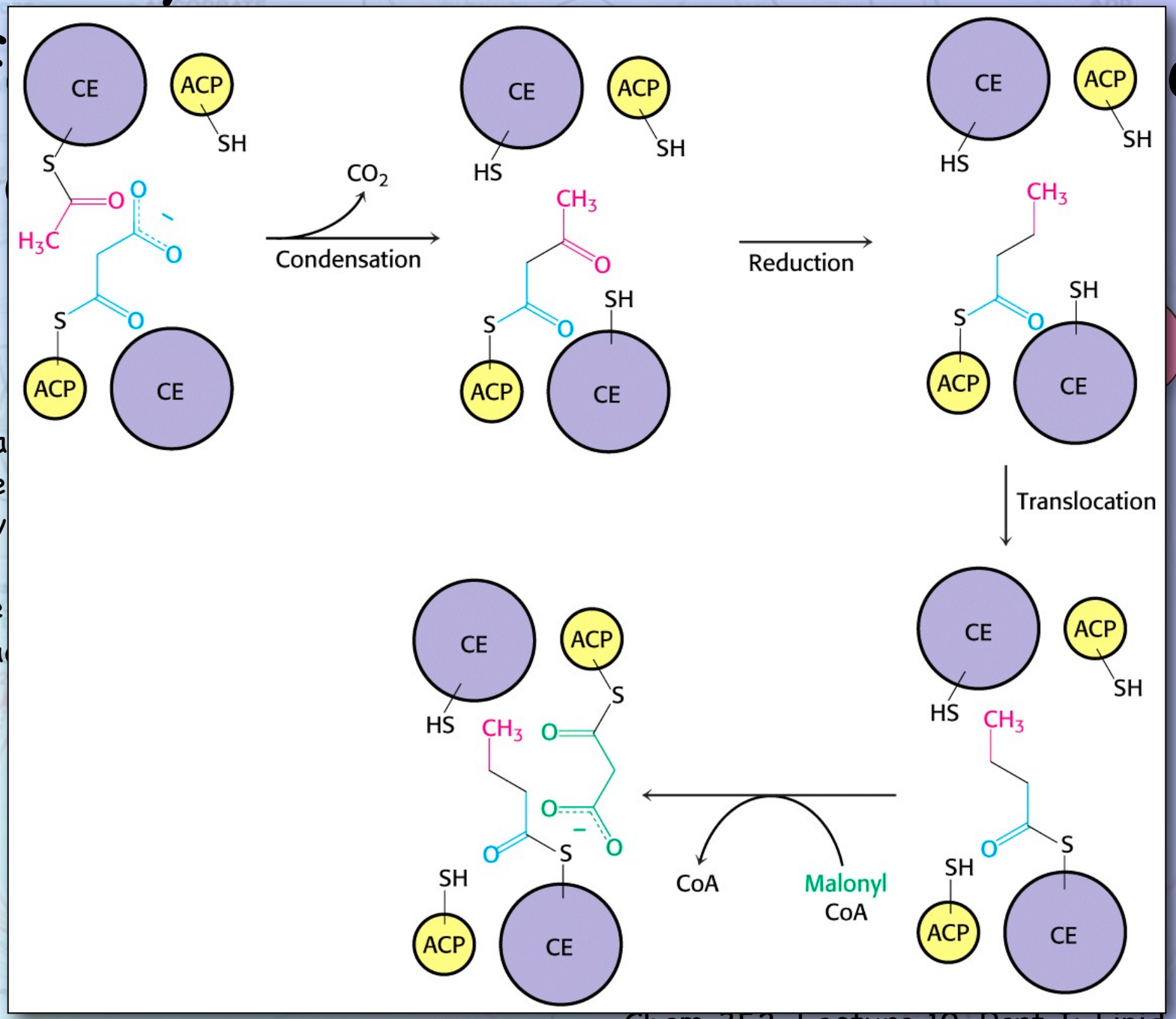

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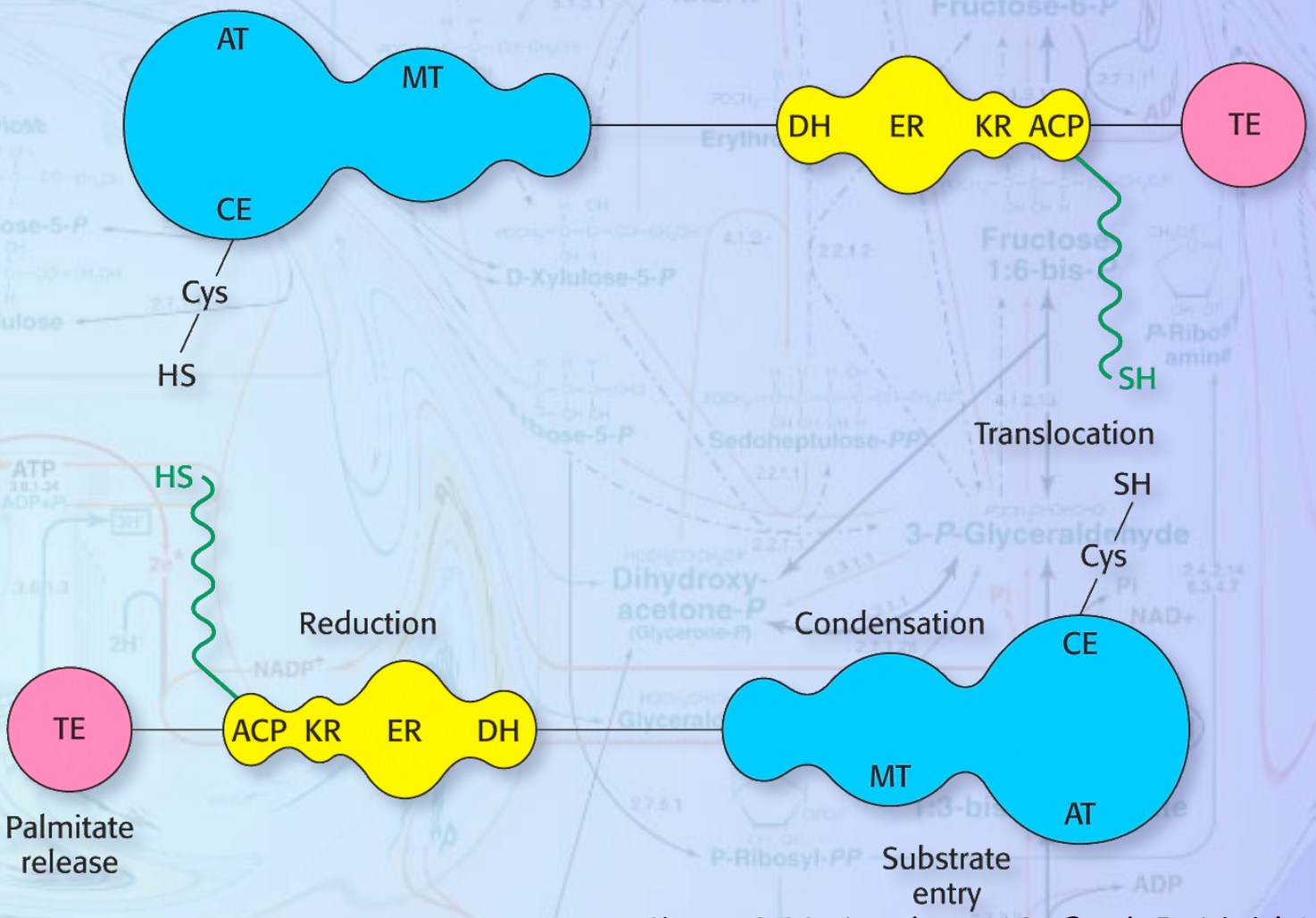

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Fatty Acid Synthesis

After palmitic acid is synthesized it is elongated and desaturated to form other fatty acids

Fatty Acid Synthesis

In eukaryotes, the acetyl-CoA for fatty acid synthesis in the cytosol comes from the mitochonrial matrix.

- The citrate/pyruvate shuttle is one of the systems used to move acetyl-CoA out into the cytosol.

Fatty Acid Synthesis

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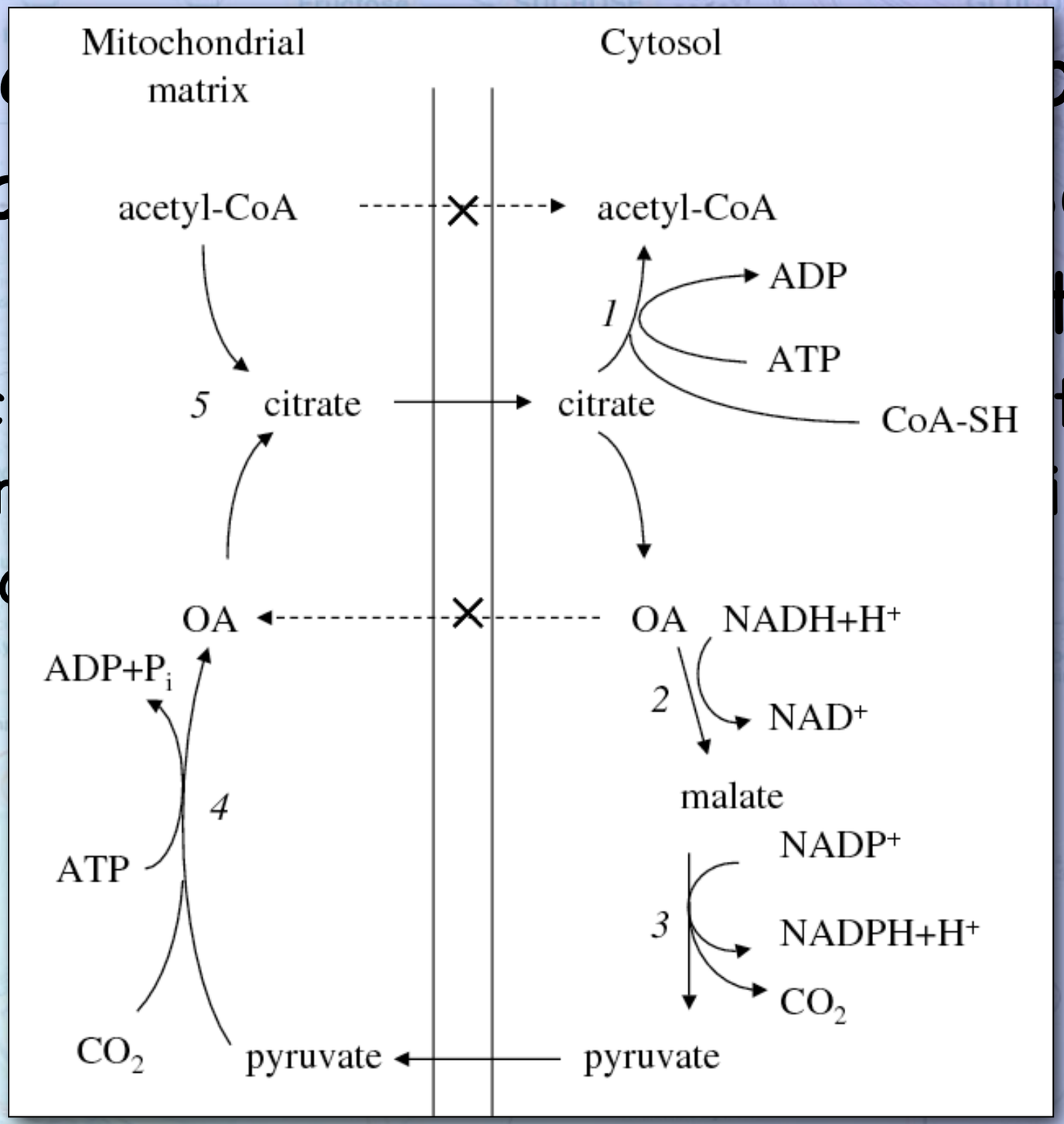

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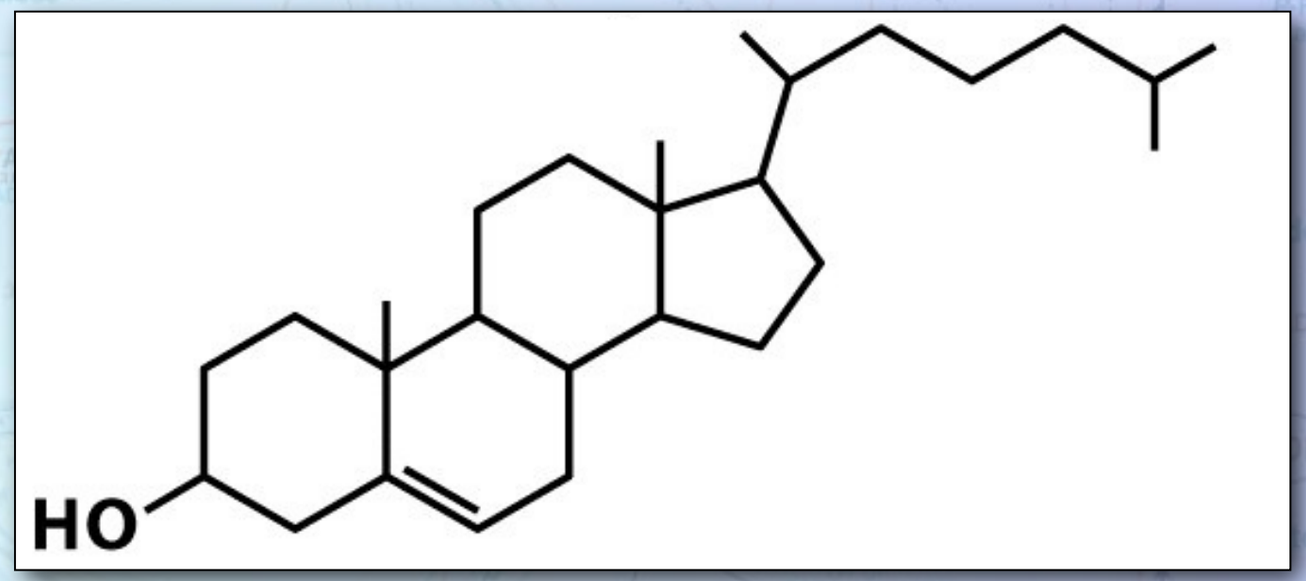
Cholesterol Synthesis

Cholesterols is used to modulate the physical properties of membranes in animals

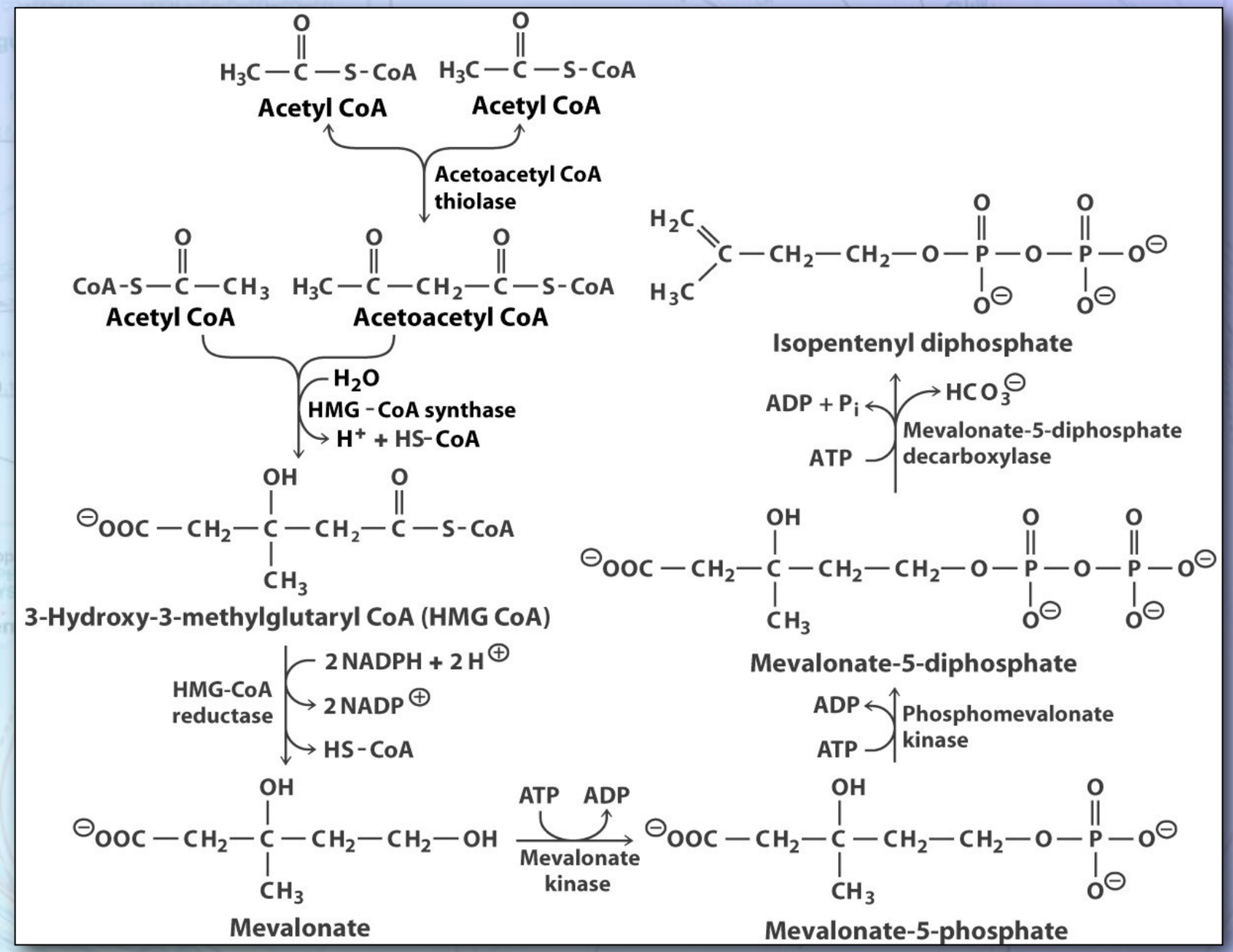
- It is also the starting point for the synthesis of all other steroid molecules

Acetate (C_2) ⟶ Isoprenoid (C_5) ⟶ Squalene (C_{30}) ⟶ Cholesterol (C_{27})



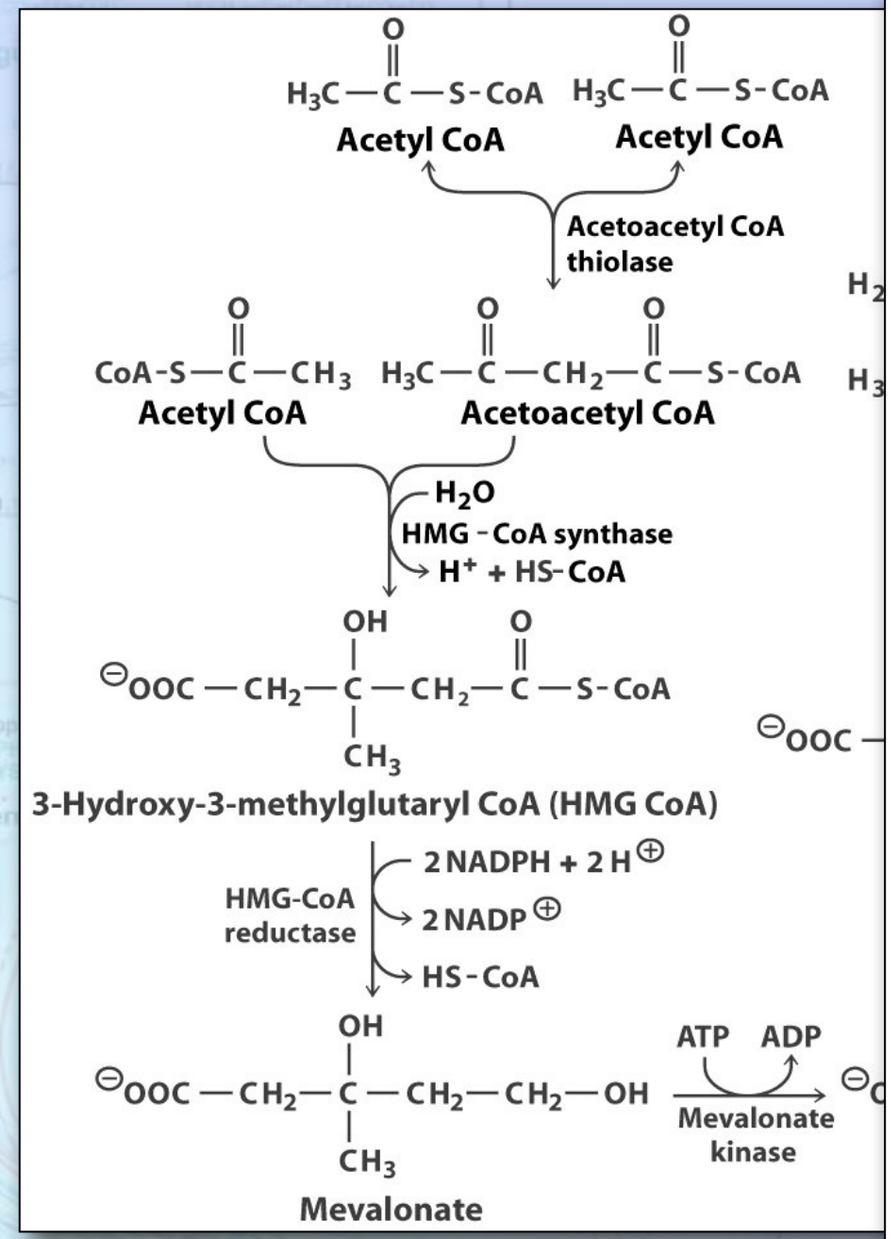
Cholesterol Synthesis

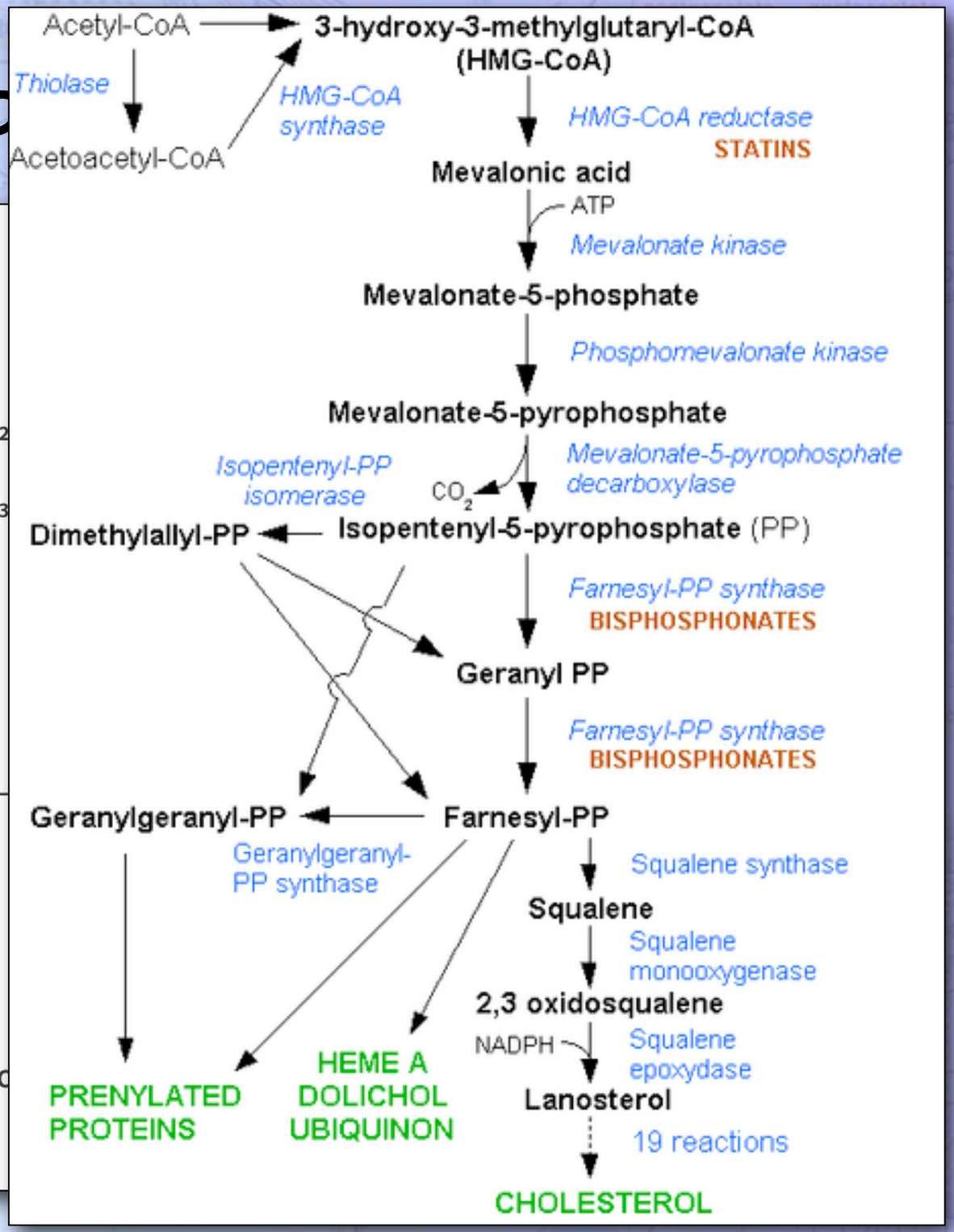
Acetate to Isoprenoid



Cholesterol Synthesis

Acetate to Isoprenoic





Cholesterol Synthesis

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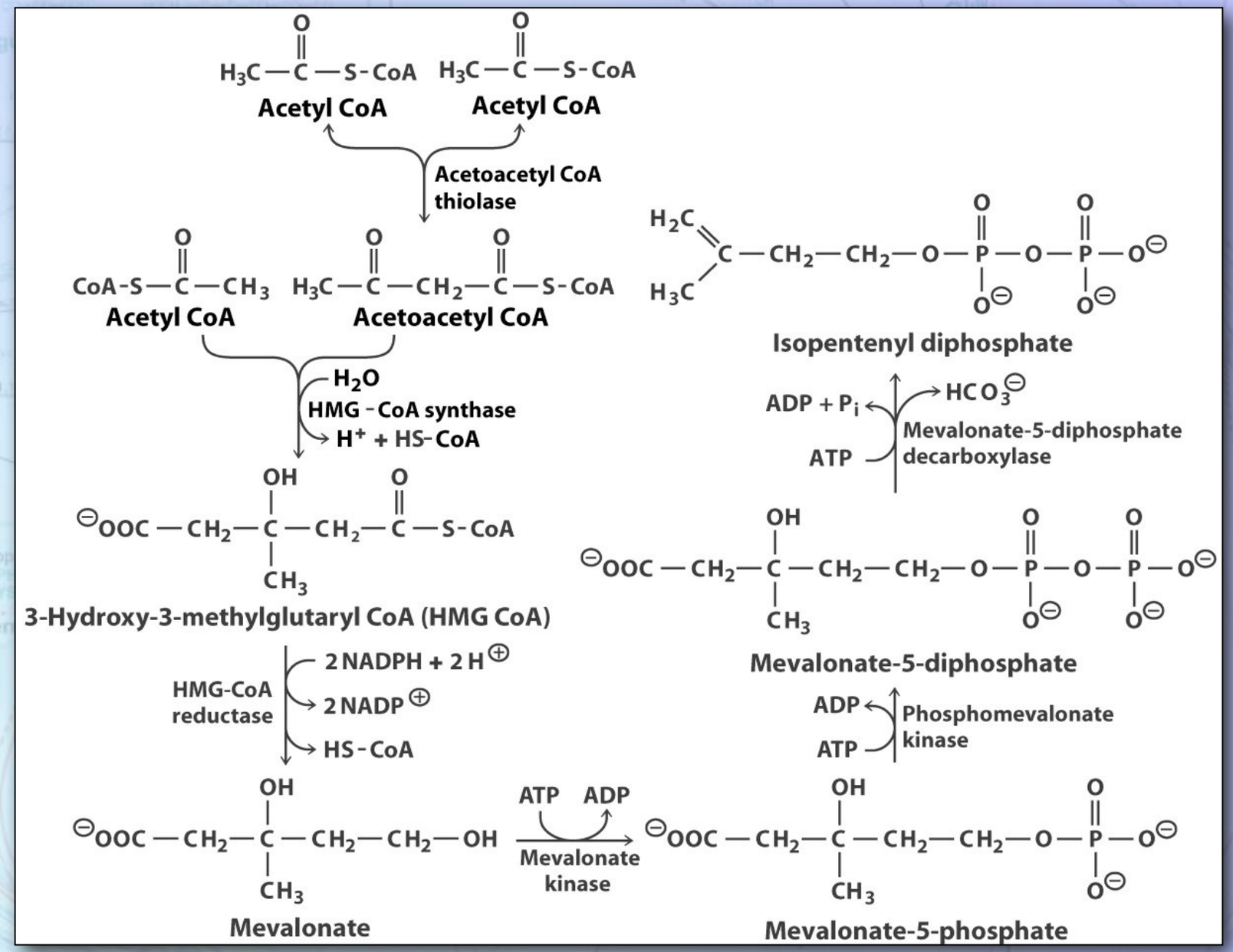
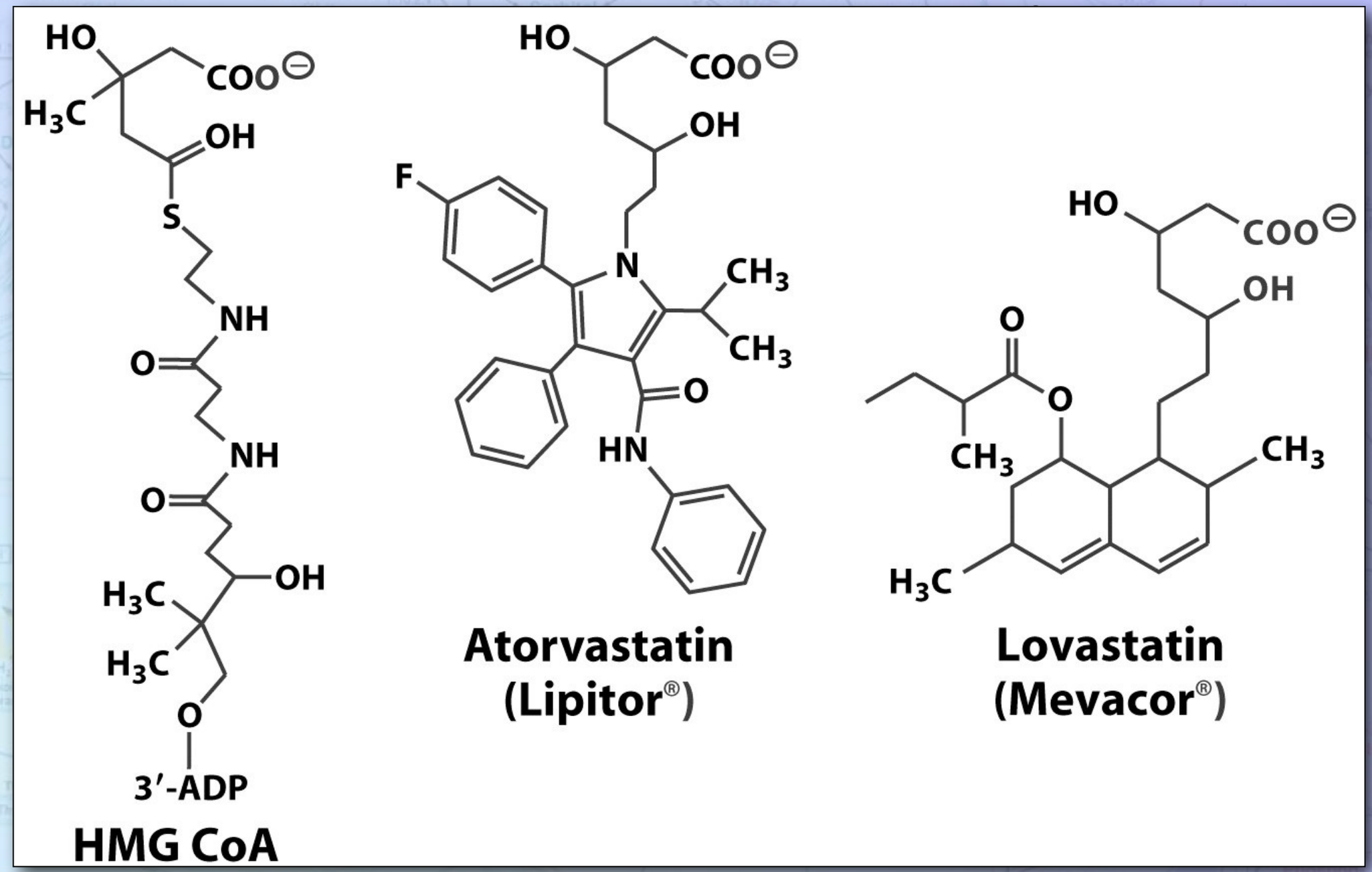


Cholesterol Synthesis

Statin (anticholesterol) drugs.



Cholesterol Synthesis

Isoprenoid to Squalene

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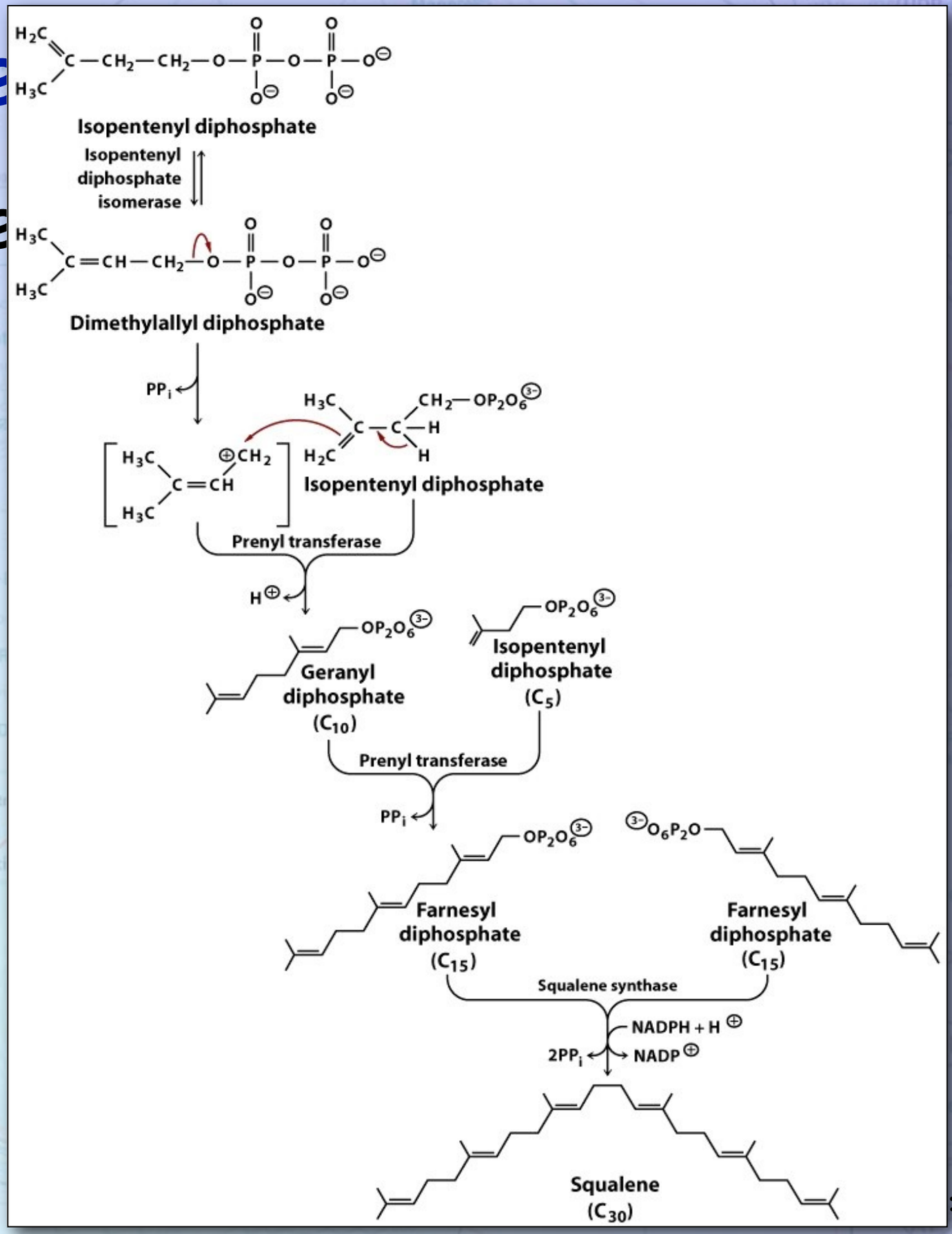
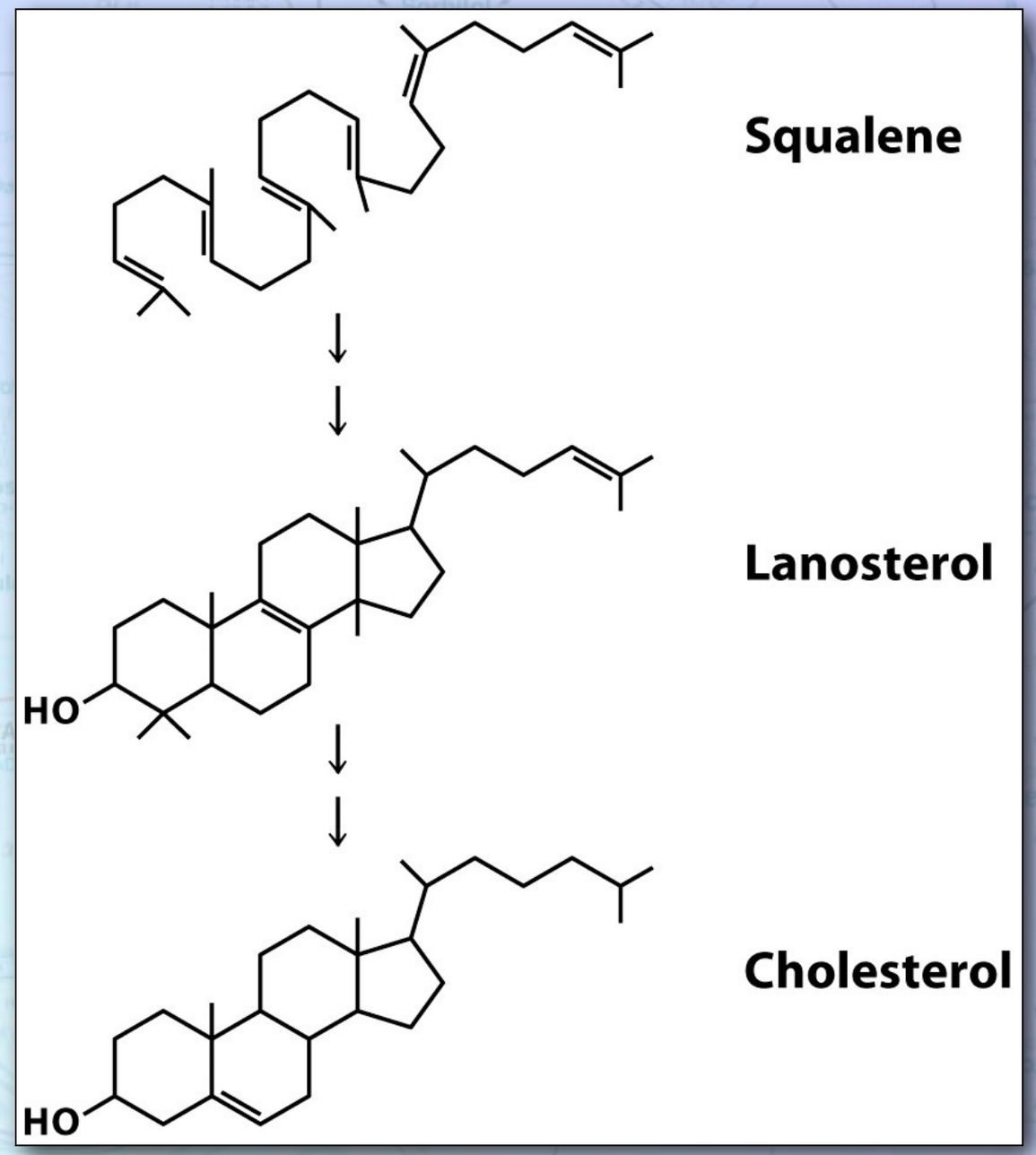


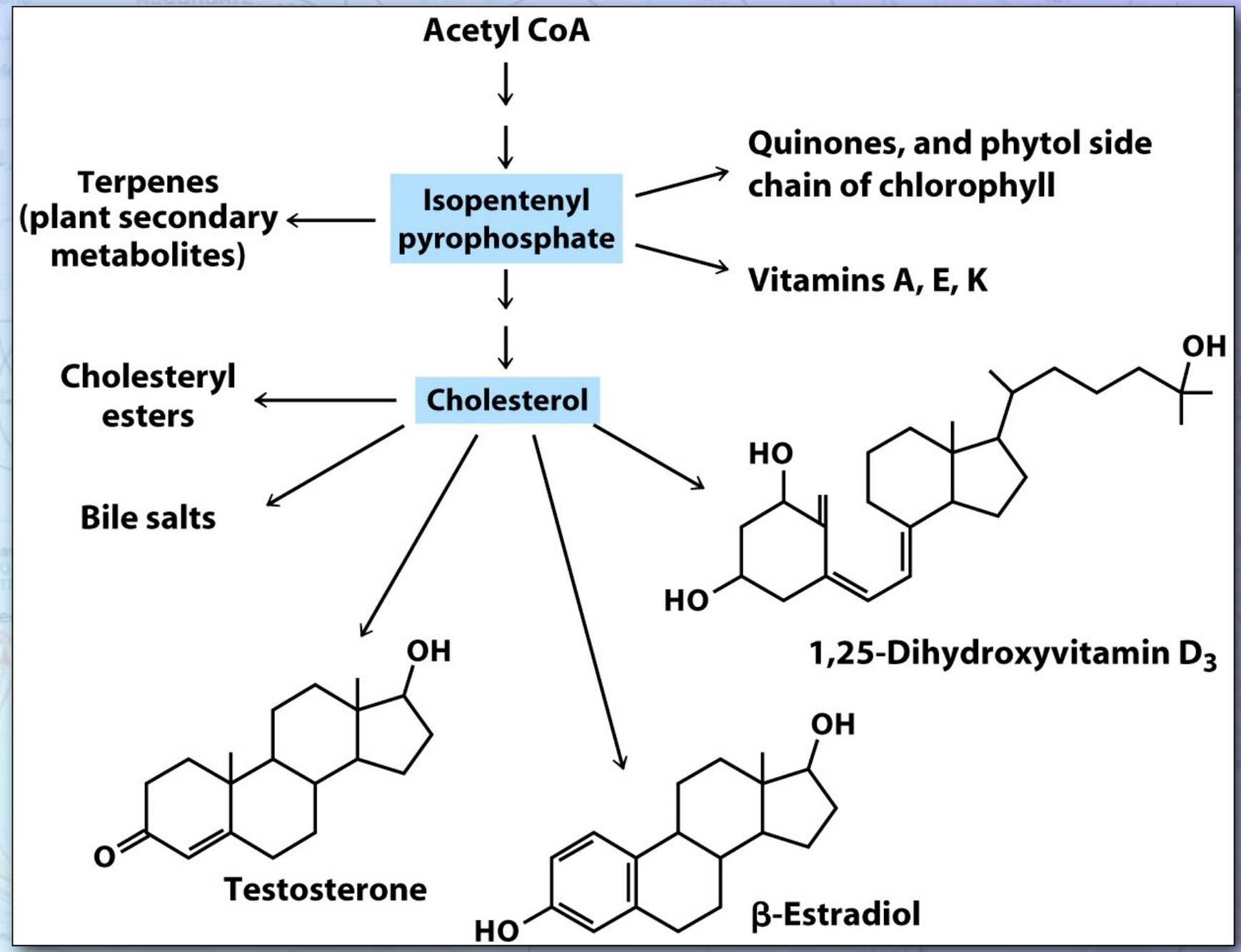
Cholesterol Synthesis

Squalene to Cholesterol



Cholesterol Synthesis

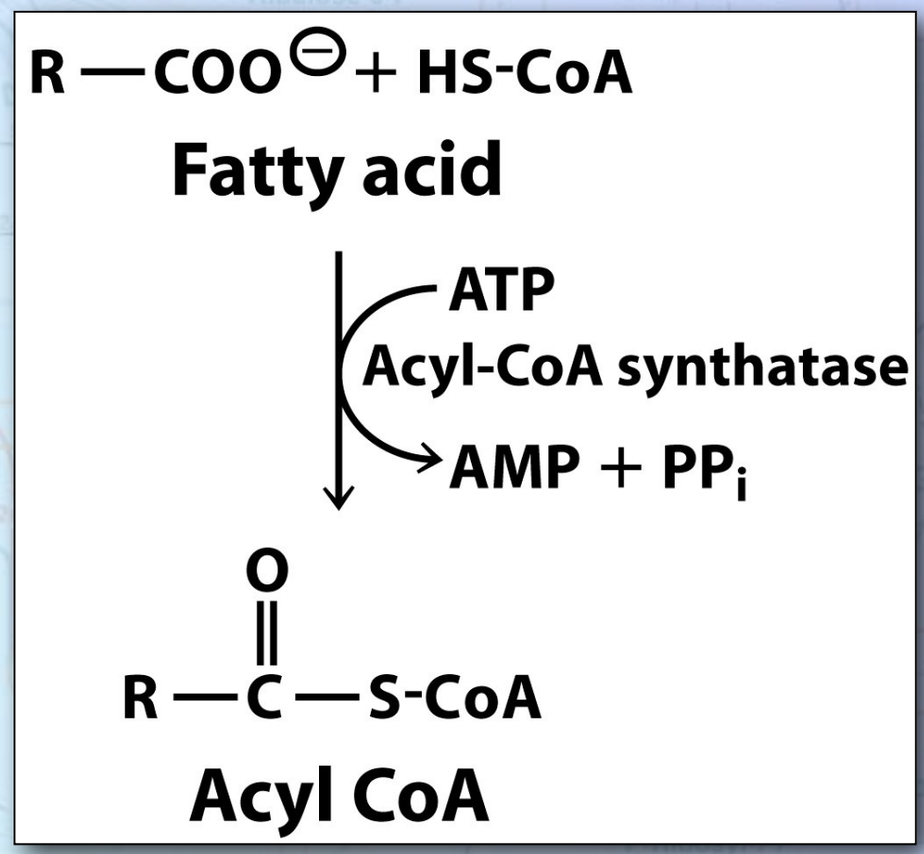
Cholesterol to other steroids



Fatty acid oxidation

The catabolism of fatty acids takes place in the mitochondria

- The fatty acid must first be activated to an acyl-CoA



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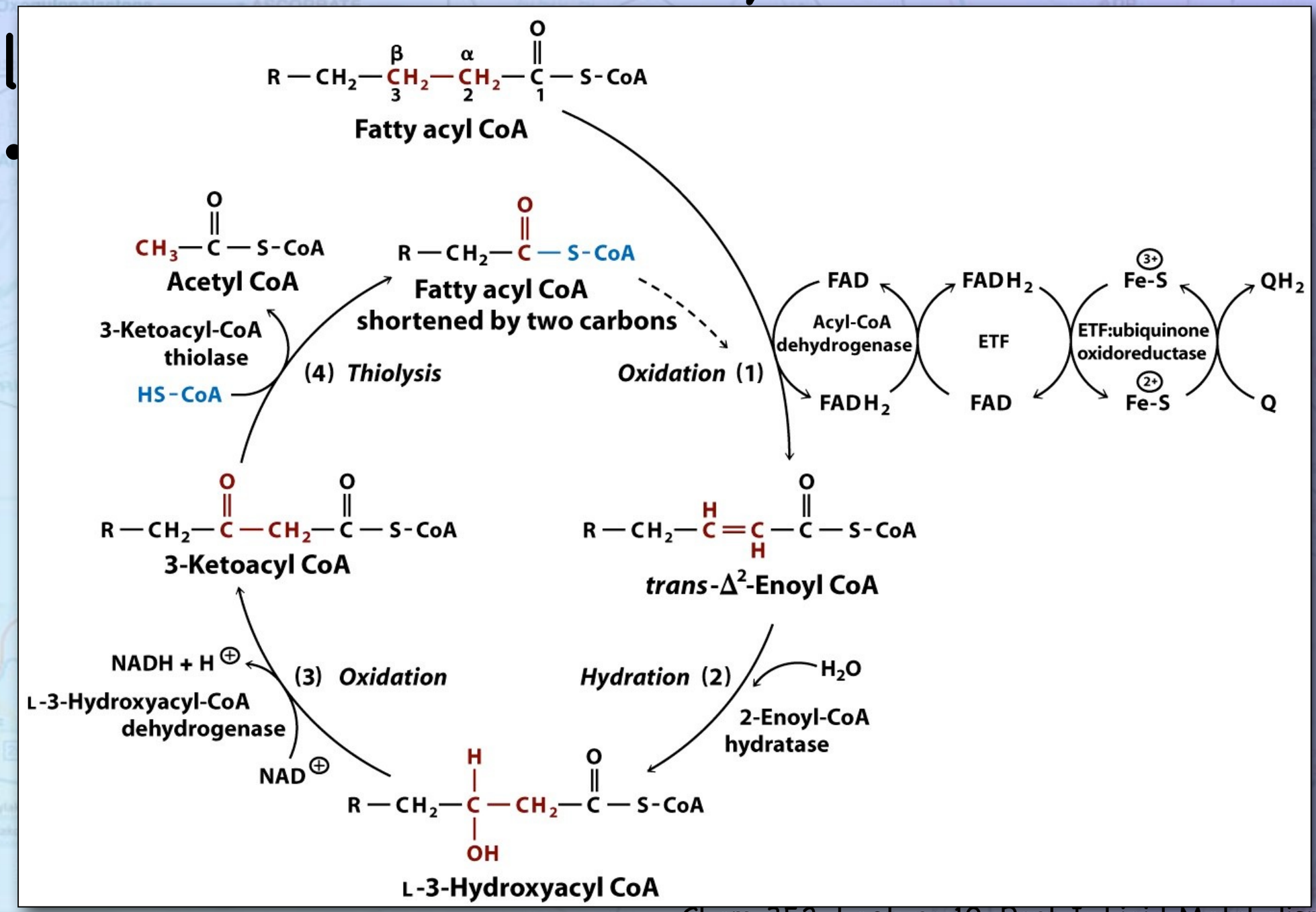

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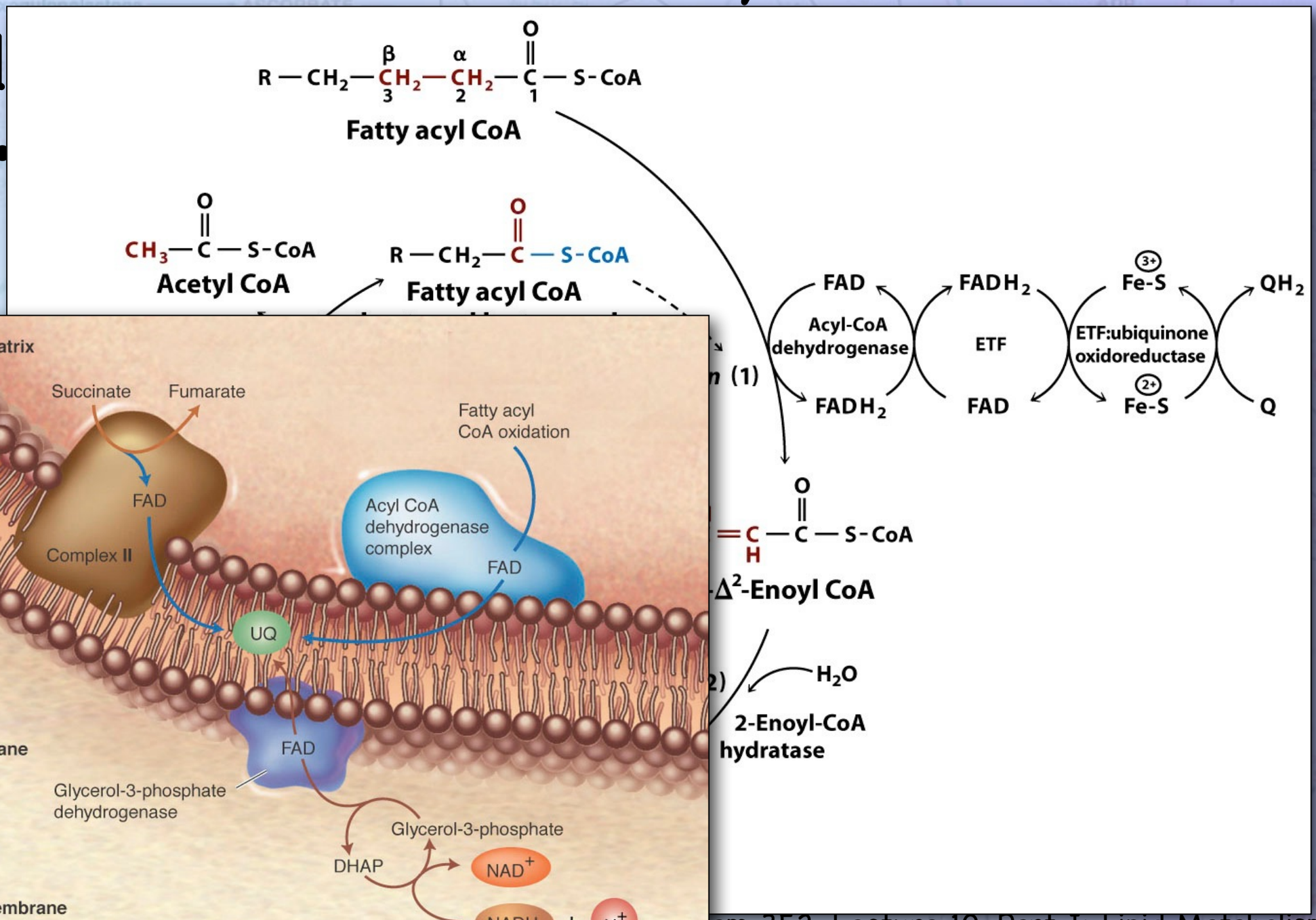

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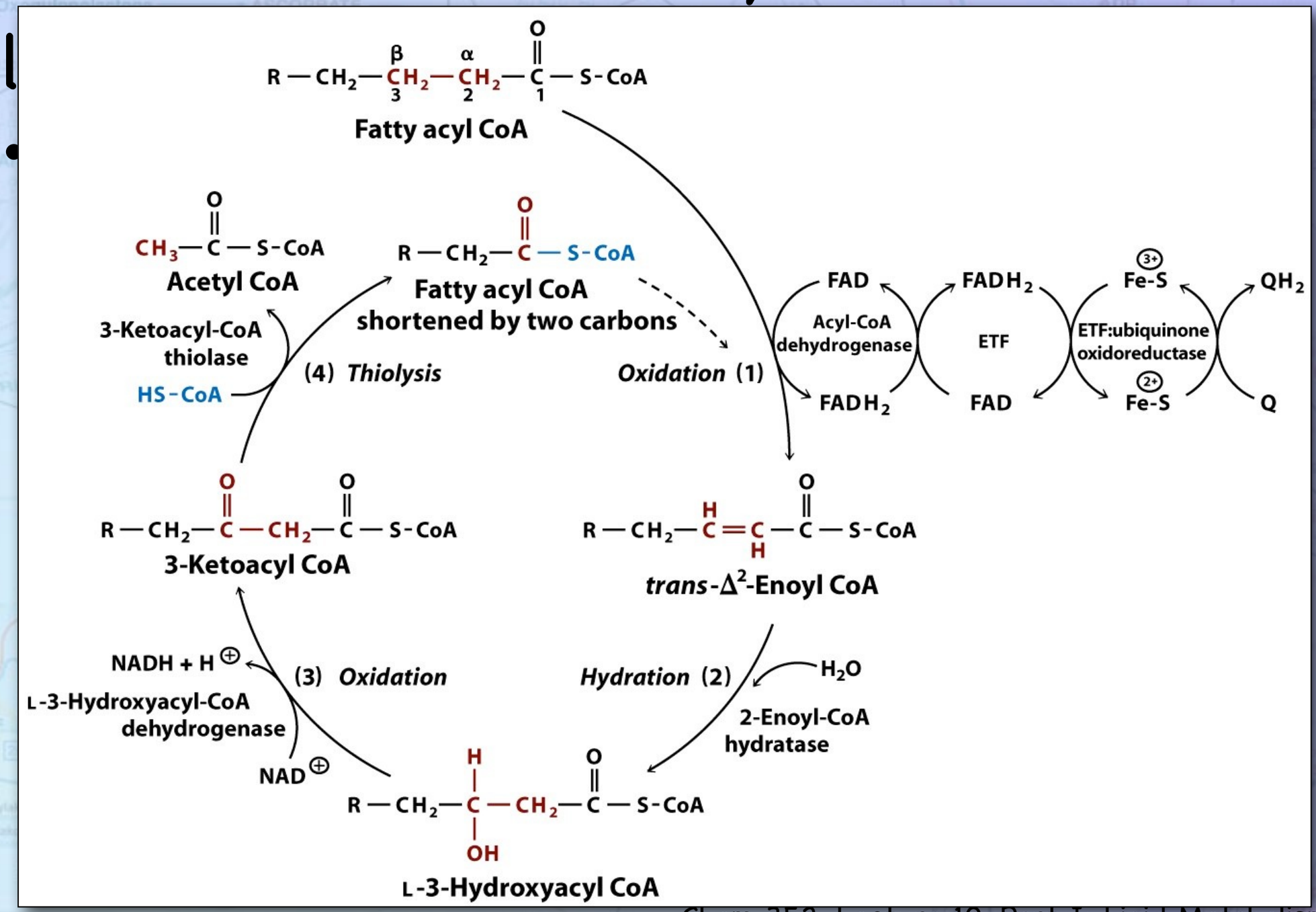

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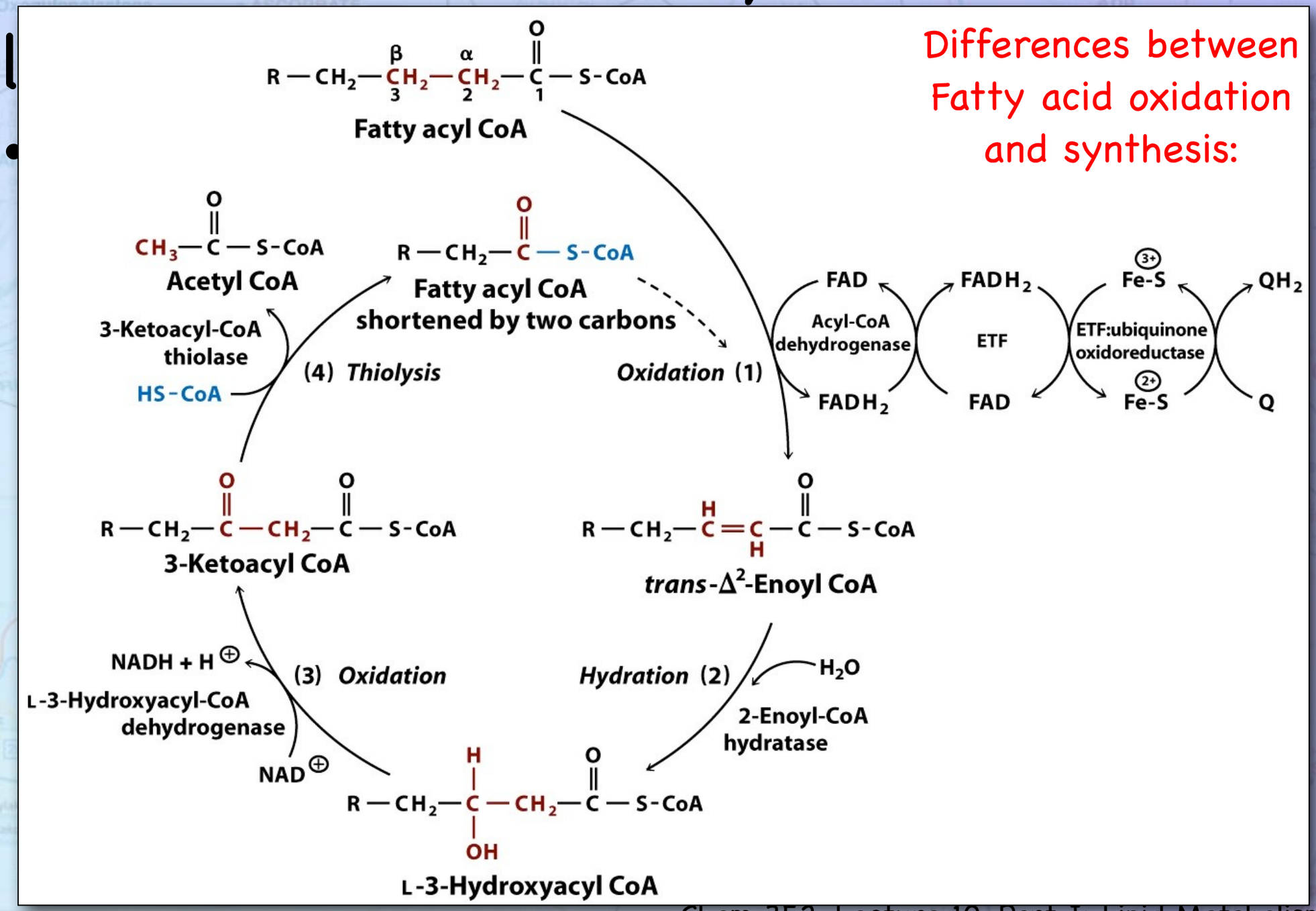

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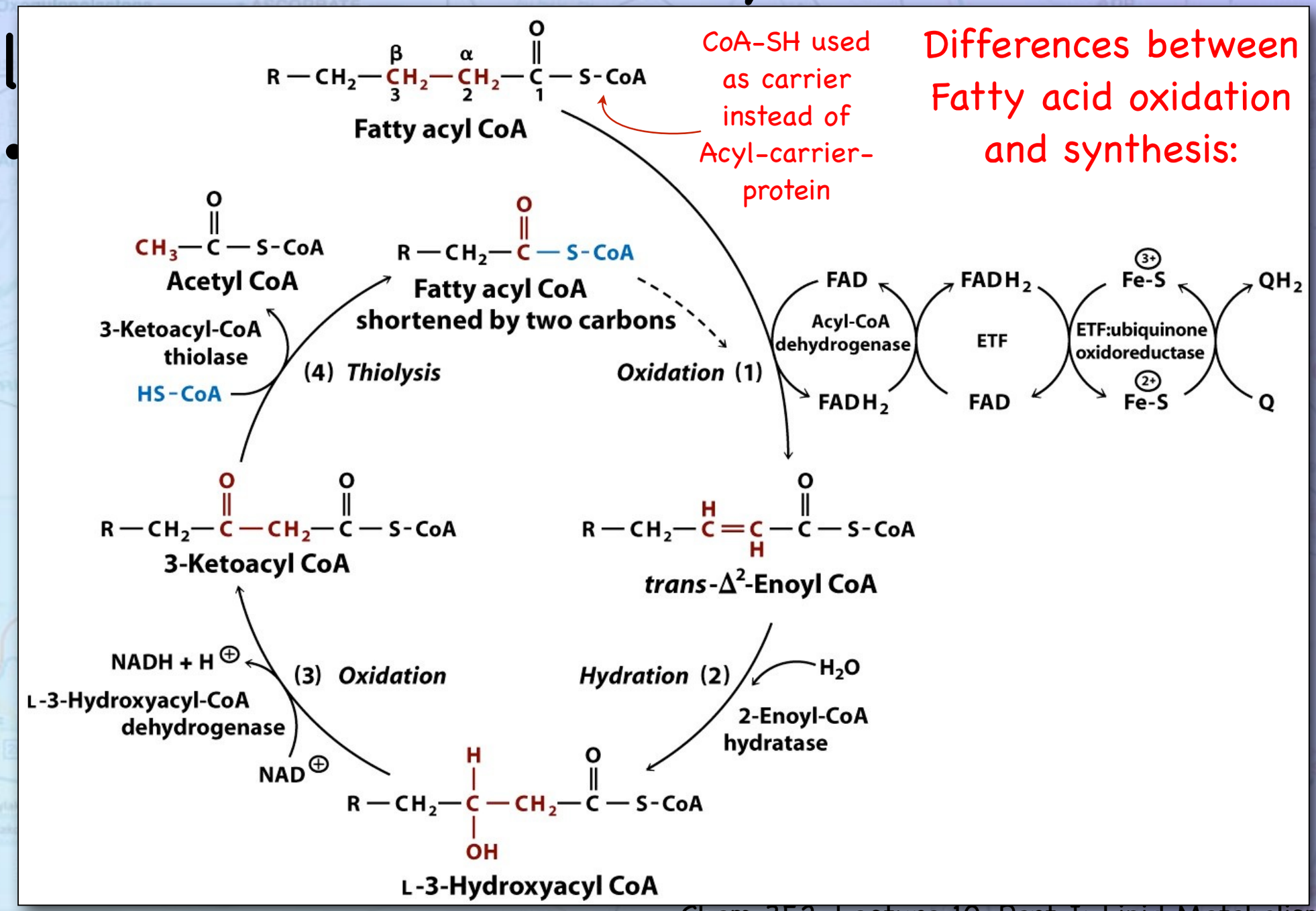

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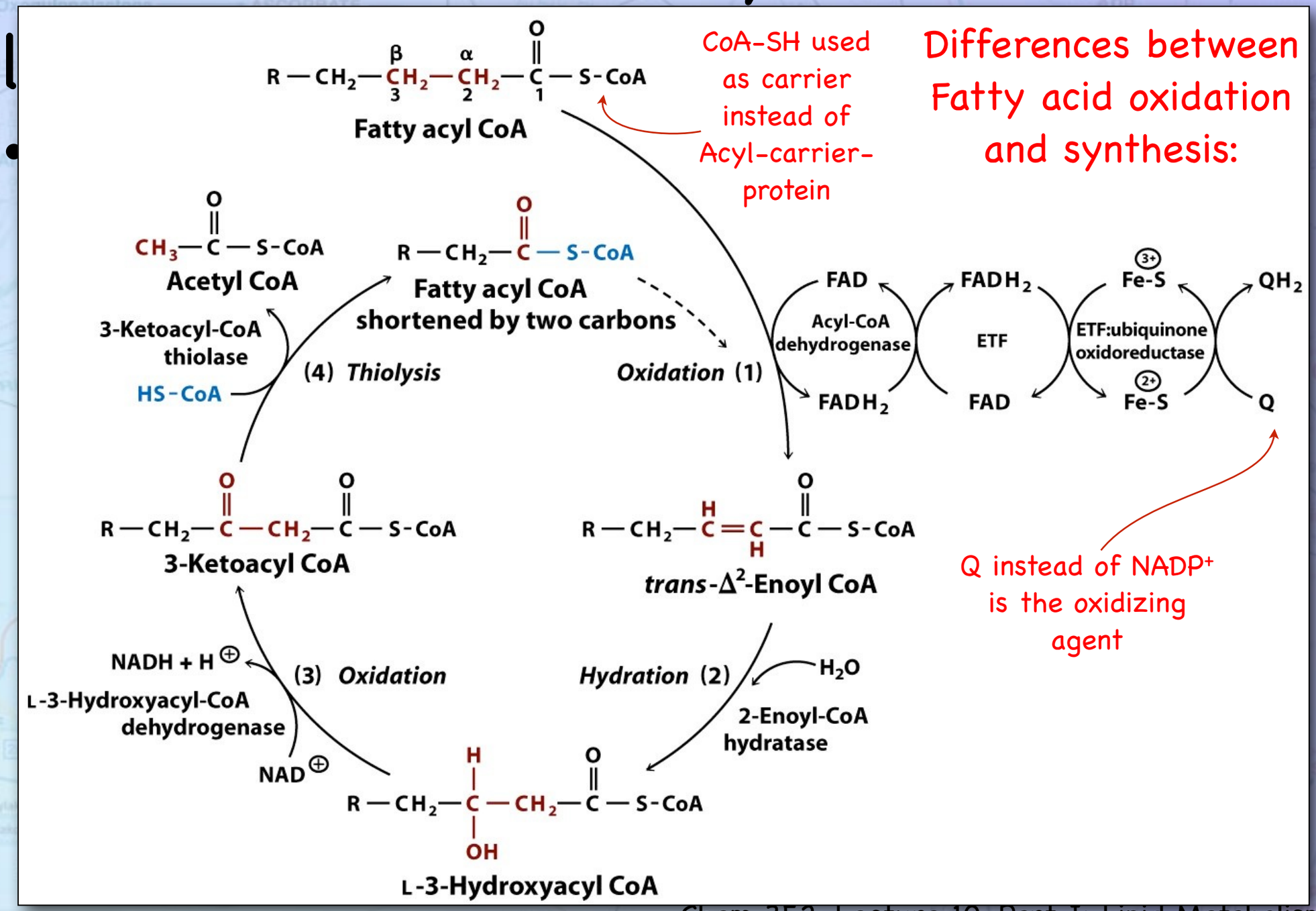

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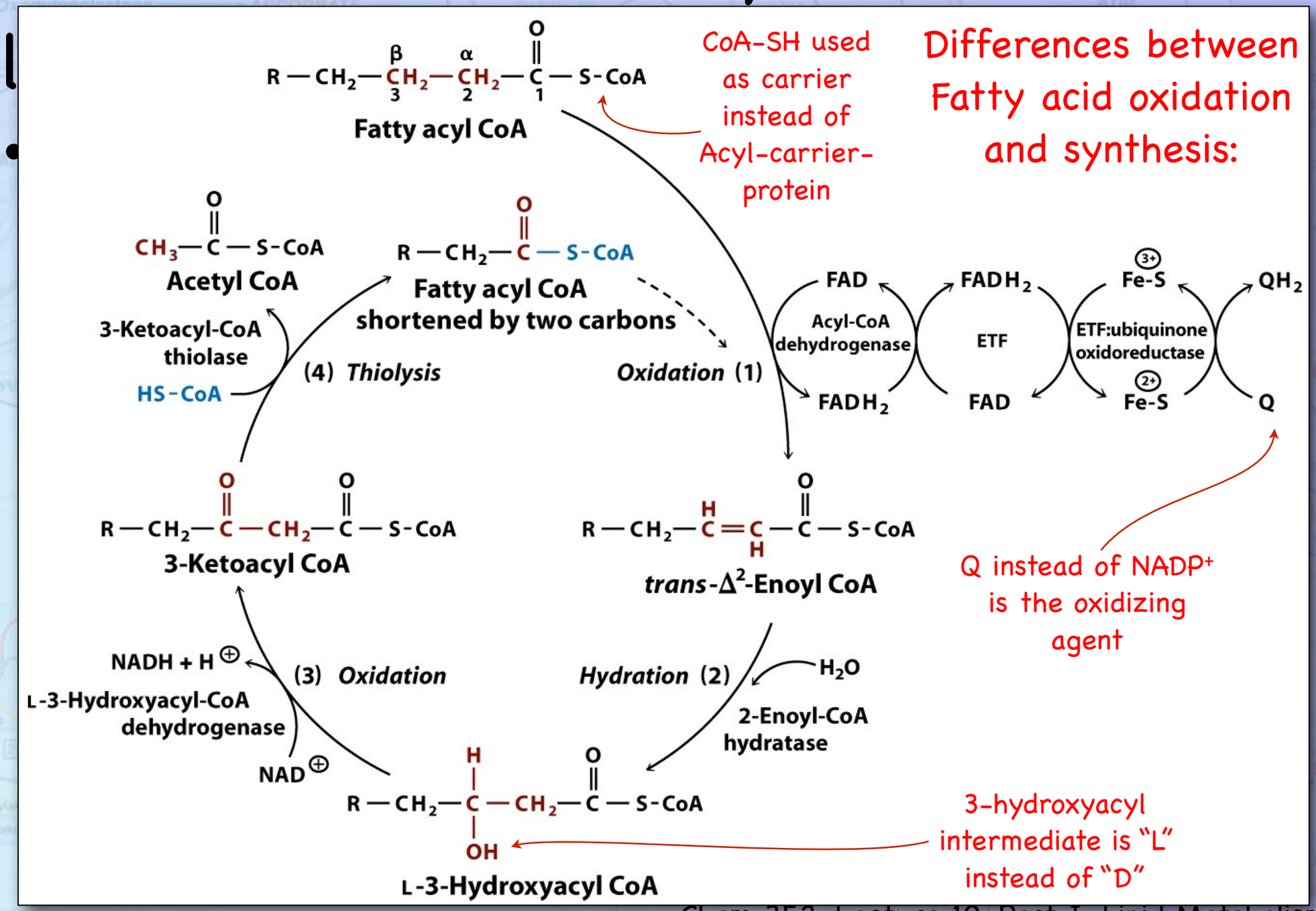

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The catabolism of fatty acids takes pl

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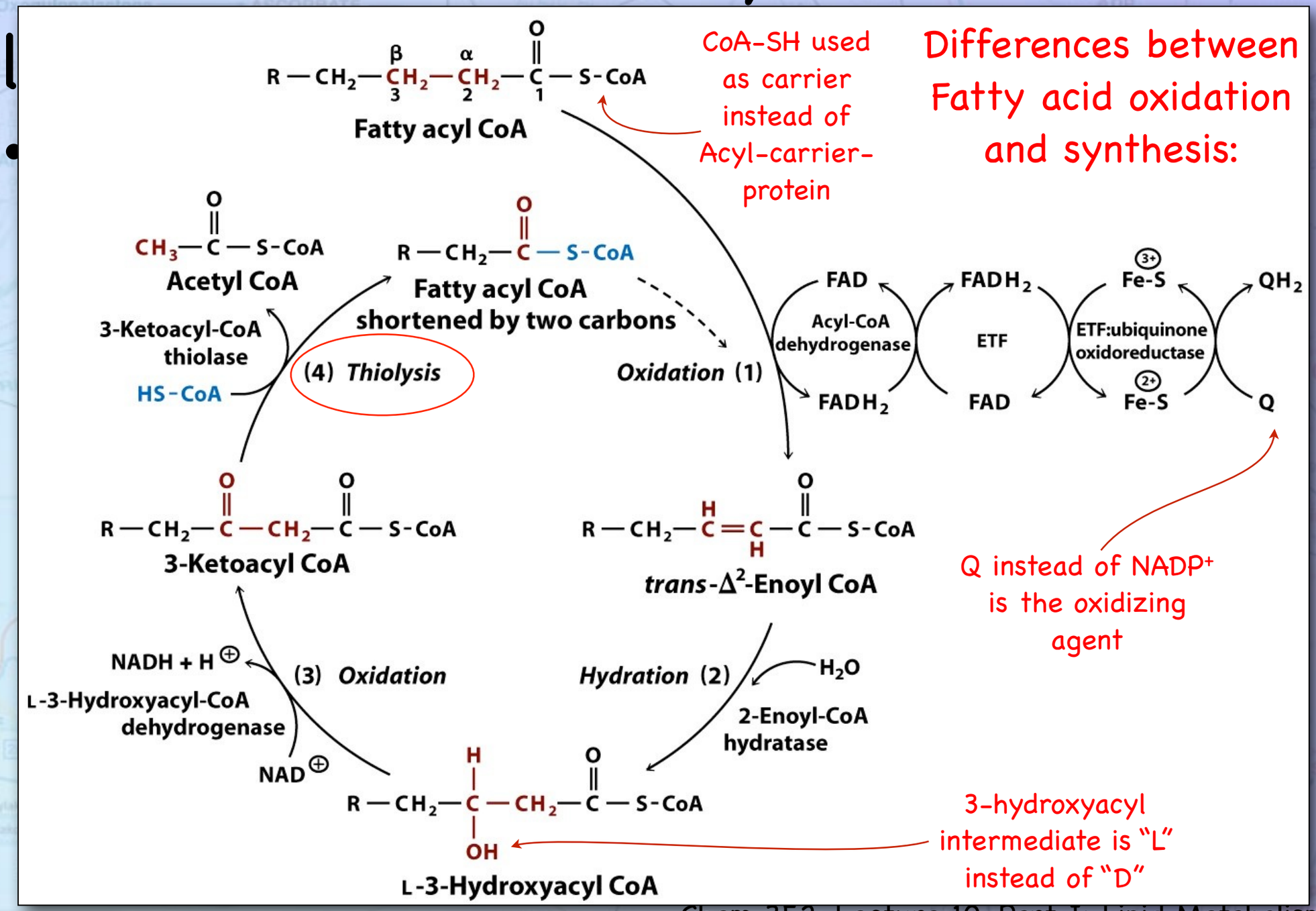
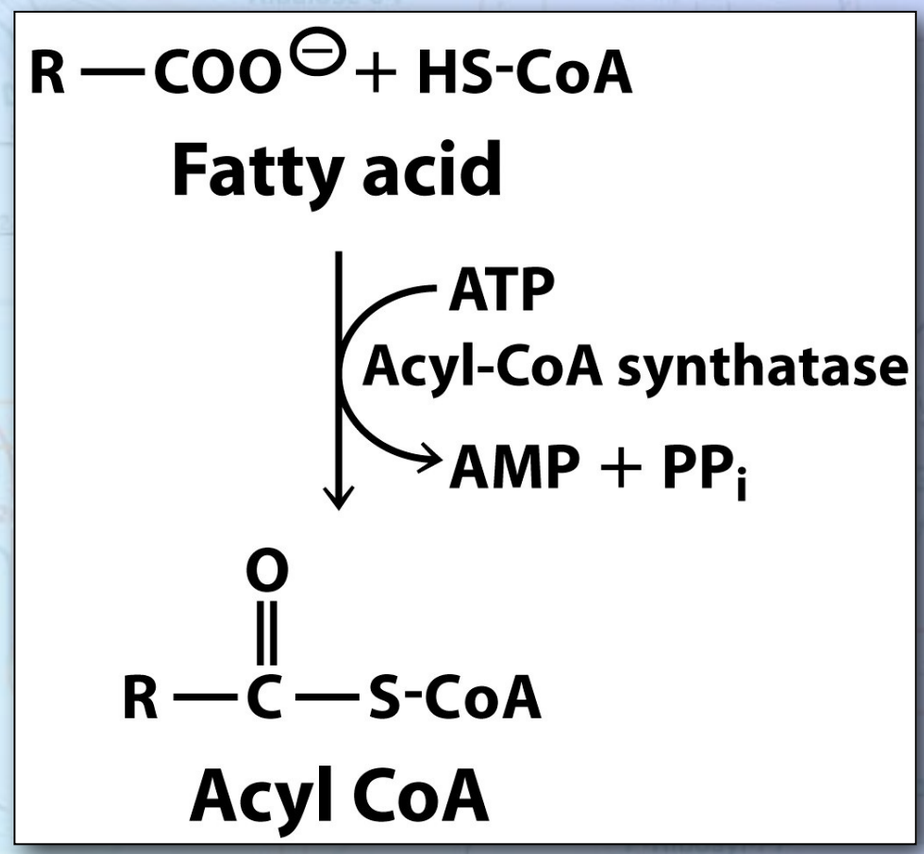


Fatty acid oxidation

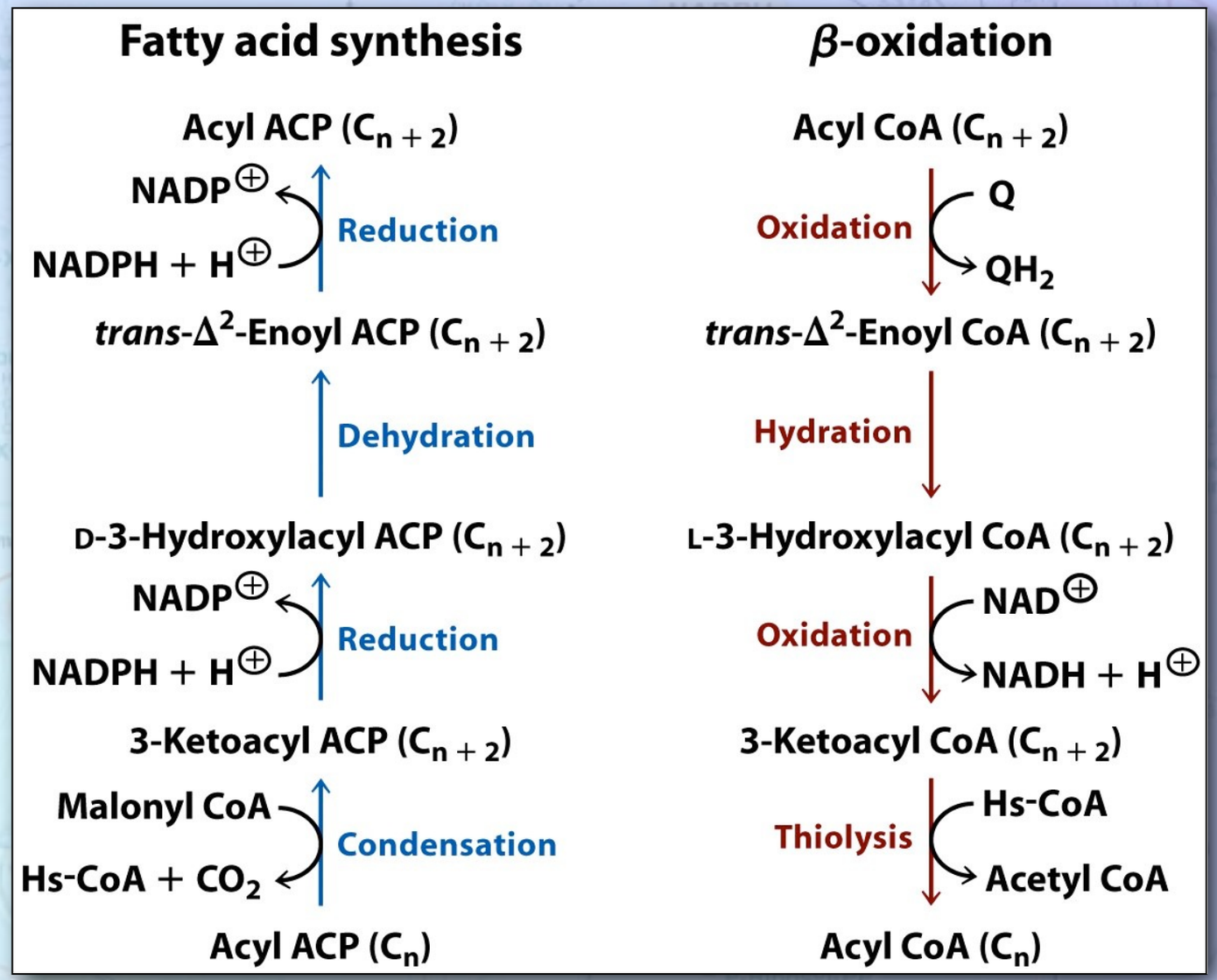
The catabolism of fatty acids takes place in the mitochondria

- The fatty acid must first be activated to an acyl-CoA



Fatty acid oxidation

In many respects it is the reverse of fatty acid synthesis.



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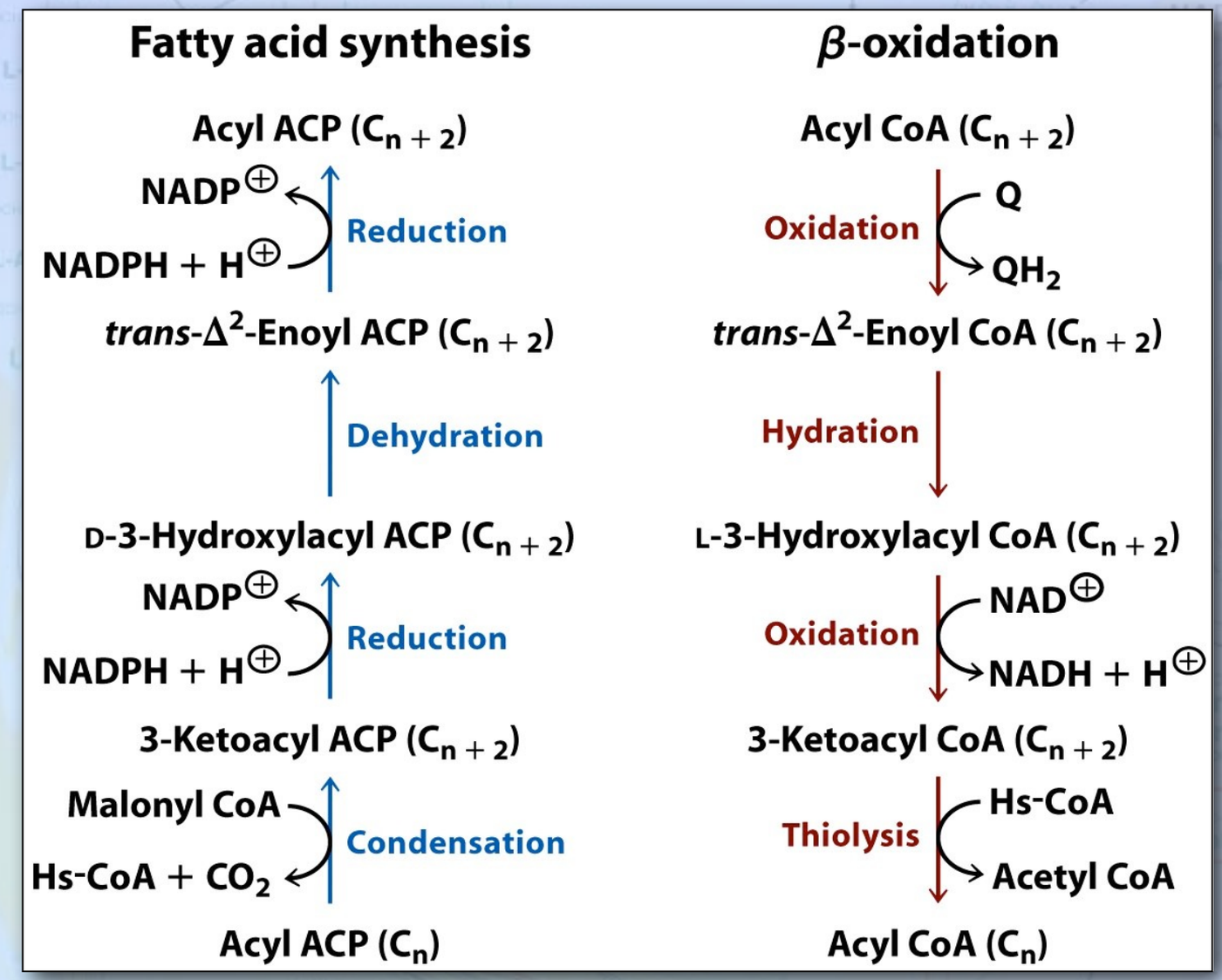
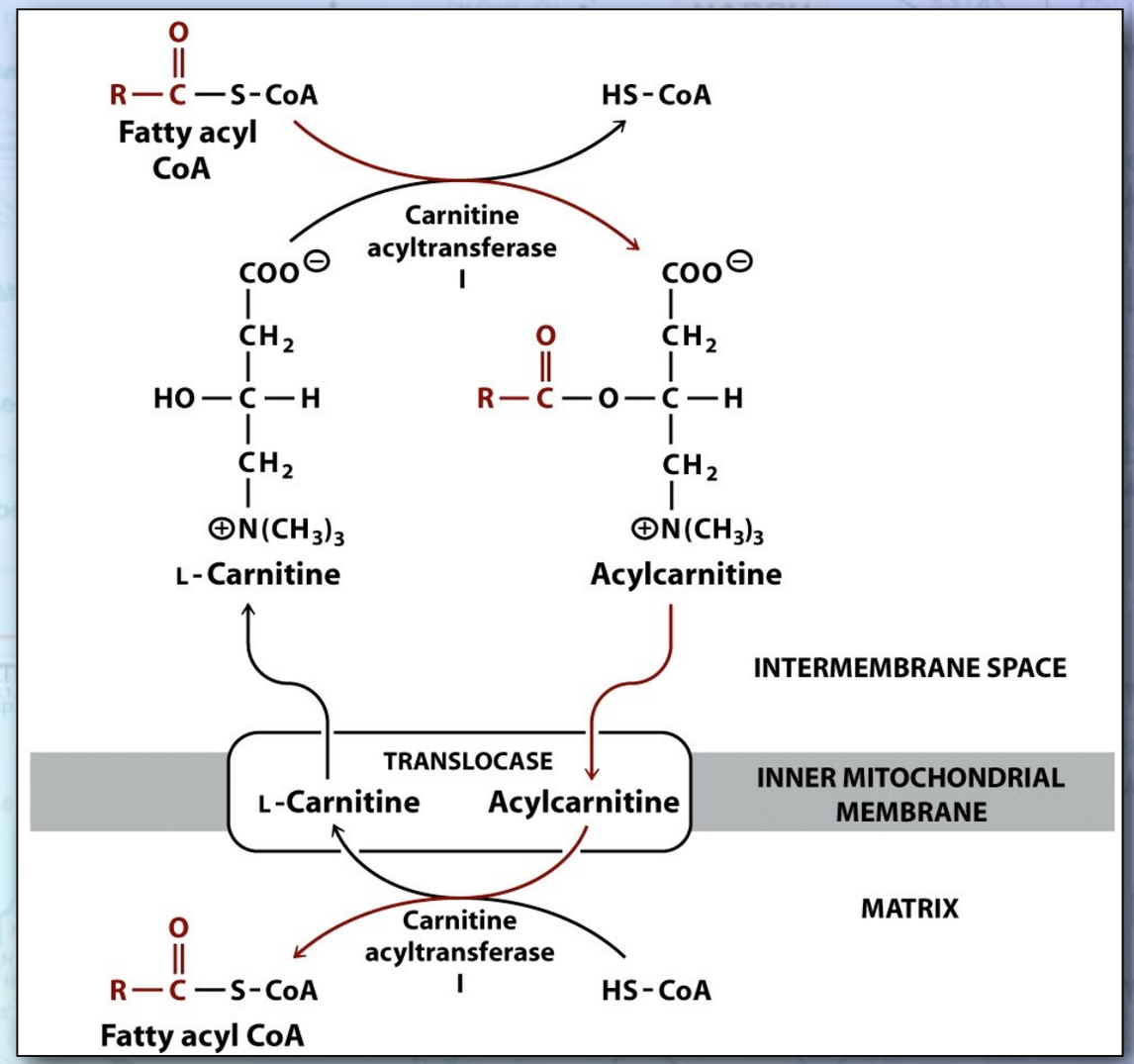


Synthesis	Oxidation
Cytosol	Mitochondria
NADPH	NAD^+ and Q
Acyl–ACP	Acyl–CoA
D–3–Hydroxy–	L–3–Hydroxy–

Fatty acid oxidation

Fatty acids enter the mitochondria by way of the carnitine shuttle.



ATP Generation

ATP generation of the the complete oxidation of stearic acid (18:0)

Stearoyl-CoA + 8 CoA-SH + 8 Q + 8 NAD^+ → 9 Acetyl-CoA + 8 QH_2 + 8 NADH + 8 H^+

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ATP generation of the the complete oxidation of stearic acid (18:0)

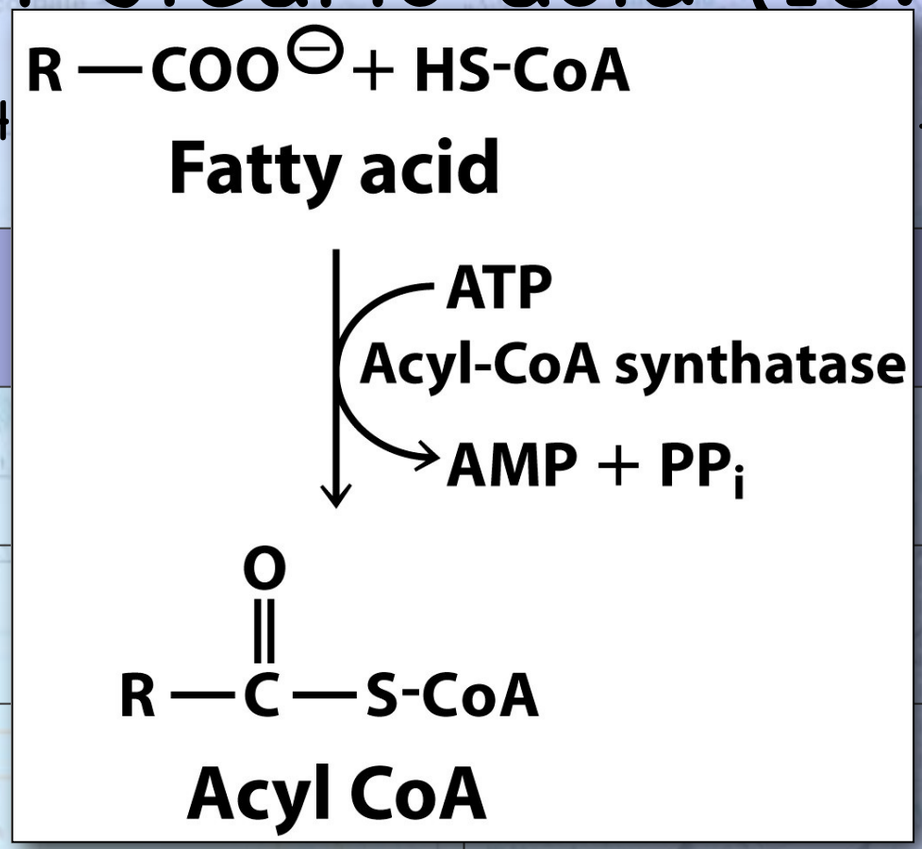
Stearoyl-CoA + 8 CoA-SH + 8 Q + 8 NAD^+ → 9 Acetyl-CoA + 8 QH_2 + 8 NADH + 8 H^+

Source	ATP's
8 QH_2	12
8 NADH	20
9 Acetyl-CoA	90
Activation of Stearate	-2
Total	**120**

ATP Generation

ATP generation of the the complete oxidation of stearic acid (18:0)

Stearoyl-CoA + 8 CoA-SH + 8 FAD + 8 QH_2 + 8 NADH + 8 H^+



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ATP Generation

ATP generation of the the complete oxidation of steric acid (18:0)

- Compared to Glucose (on a per C basis)

ATP Generation

ATP generation of the the complete oxidation of steric acid (18:0)

- Compared to Glucose (on a per C basis)

Source	ATP's
3 x Glucose	3 x 32 = 96
Stearate	120

ATP Generation

ATP generation of the the complete oxidation of stearic acid (18:0)

- Compared to Fatty Acid Synthesis

ATP Generation

ATP generation of the the complete oxidation of stearic acid (18:0)

- Compared to Fatty Acid Synthesis

Source	ATP's
8 Acetyl-CoA → 8 Malonyl-CoA	8
8 Rounds 16 NADPH	40
9 Acetyl-CoA (Calvin cycle)	9 x 17 = 153
Total	**201**

ATP Generation

ATP generation of the the complete oxidation of stearic acid (18:0)

- Compared to Fatty Acid Synthesis

Source	ATP's
8 Acetyl-CoA → 8 Malonyl-CoA	8
8 Rounds 16 NADPH	40
9 Acetyl-CoA (Calvin cycle)	9 x 17 = 153
Total	**201**

Yield = 120/201 = 60%

ATP Generation

Regulation of Lipid Metabolism

- Involves same hormones as carbohydrate metabolism
  - Glucogon (fasting state)
  - Epinephrin (excited state)
  - Insulin (fed state)

ATP Generation

R

Glucagon & Epinephrine	Insulin
Activate lipases in adipose tissues	Activate formation and storage of triacylglycerides
Inactivates acetyl-CoA carboxylase Acetyl-CoA inhibits pyruvate dehydrogenase	Activate acetyl-CoA carboxylase Malonyl-CoA inhibits Carnitine acyltransferase I

ATP Generation

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Epi

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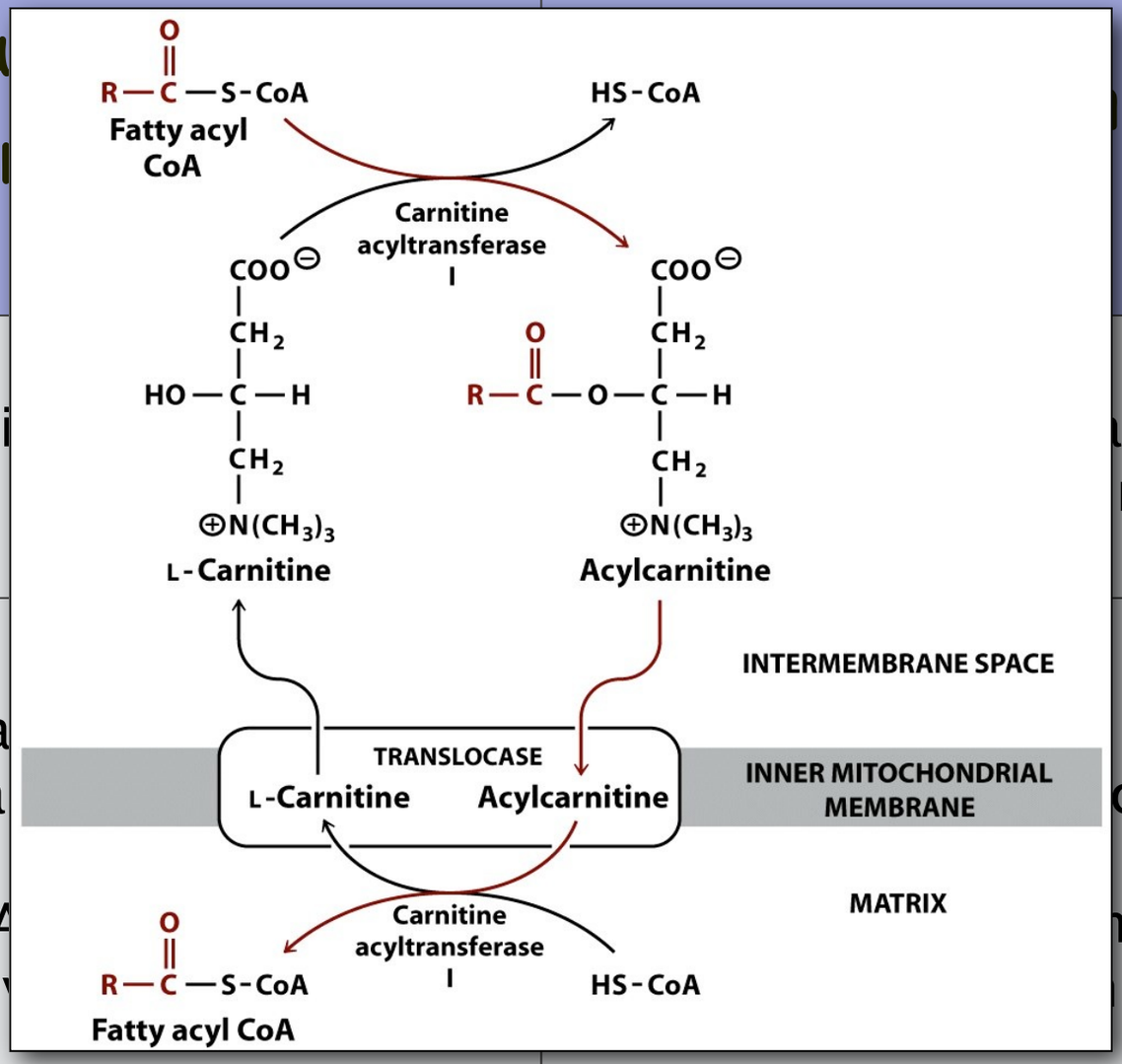

ATP Generation

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Activate lipases in adipose tissues	Activate formation and storage of triacylglycerides
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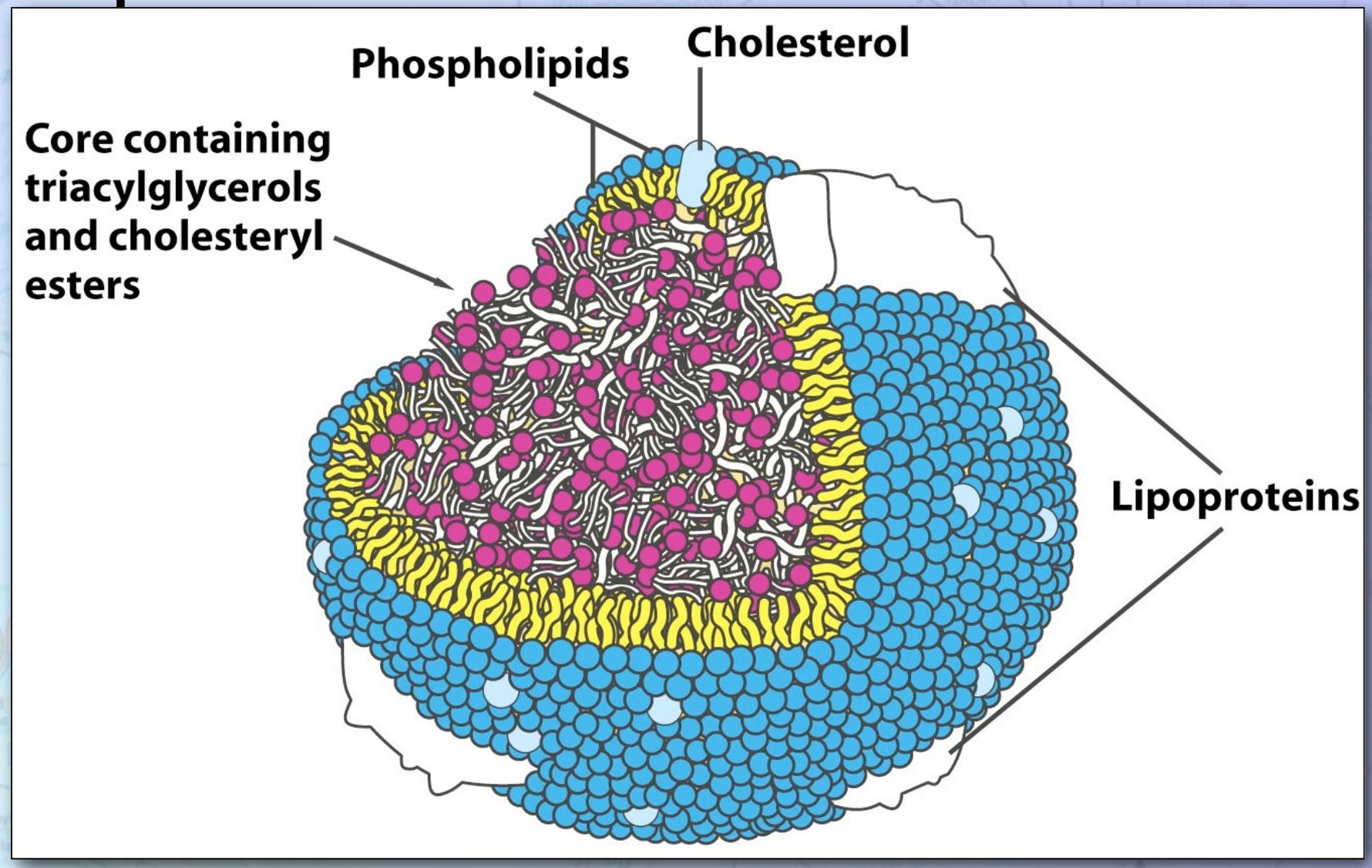
Transport of lipds in Blood

Lipids are transported by lipoprotein complexes

- Chylomicrons
- VLDH (Very Low Density Lipoproteins)
- IDH (Intermediate Density Lipoproteins)
- LDL (Low Density Lipoproteins)
- HDL (High Density Lipoproteins)

Transport of lipds in Blood

Lipids are transported by lipoprotein complexes



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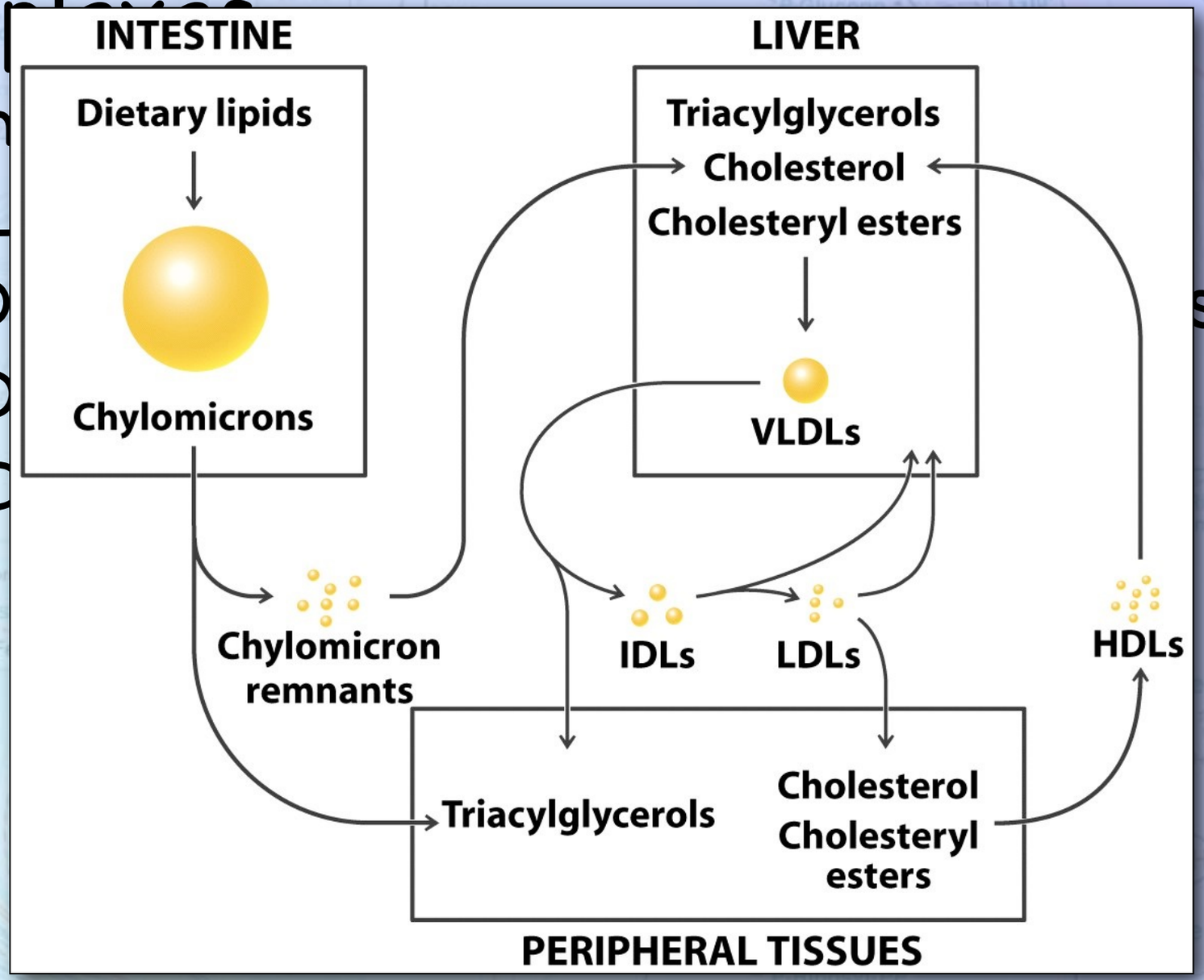
Transport of lipds in Blood

Lipids are transported by lipoprotein comp

- Ch
- VL
- ID
- LD
- HD



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Lipids are transported by lipoprotein complexes

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- LDL (Low Density Lipoproteins)
- HDL (High Density Lipoproteins)

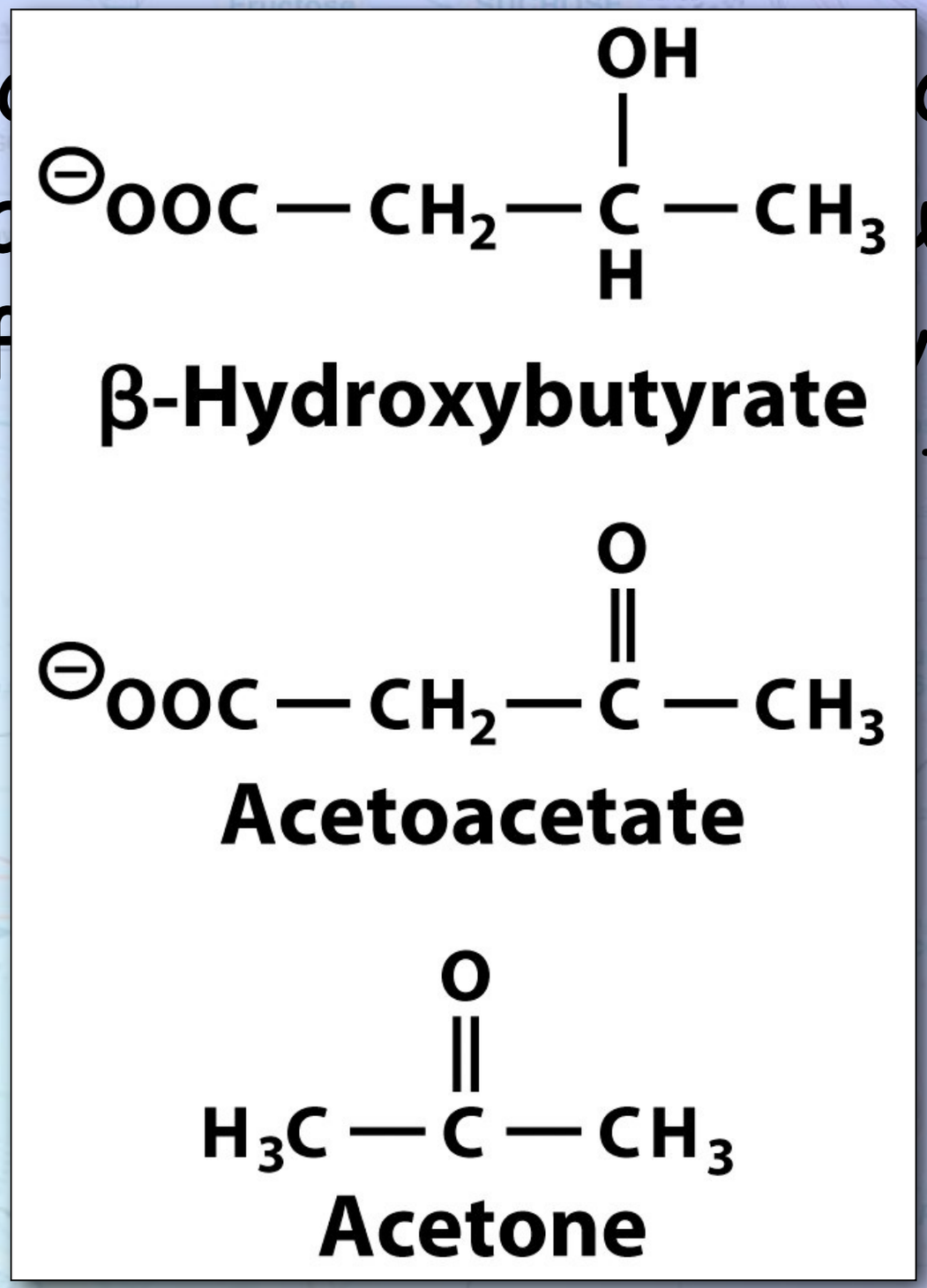
Ketone Bodies

Ketone bodies are formed from acetyl-CoA as a soluble circulating source of fat-derived energy.

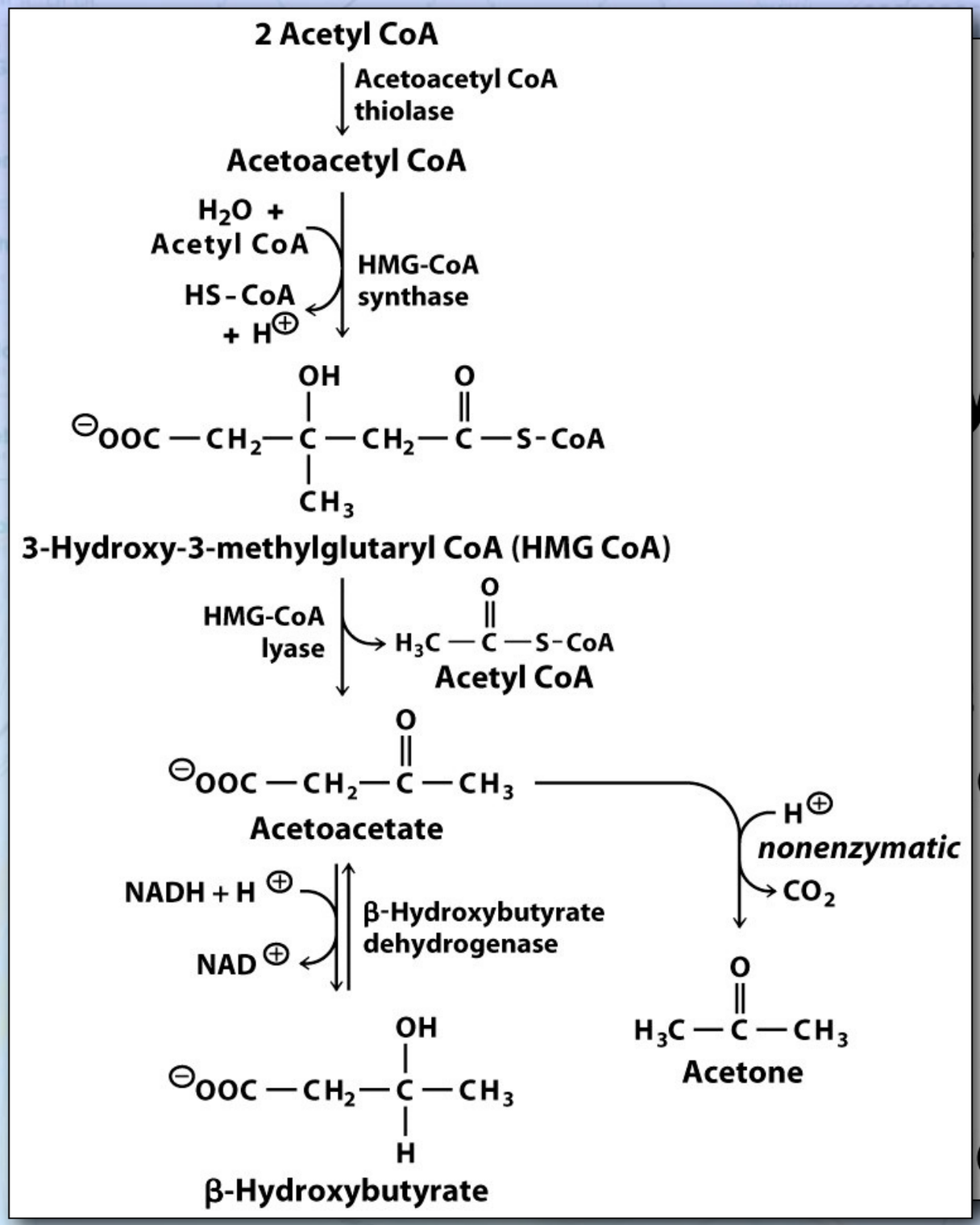
- Produce under conditions of long-term fasting

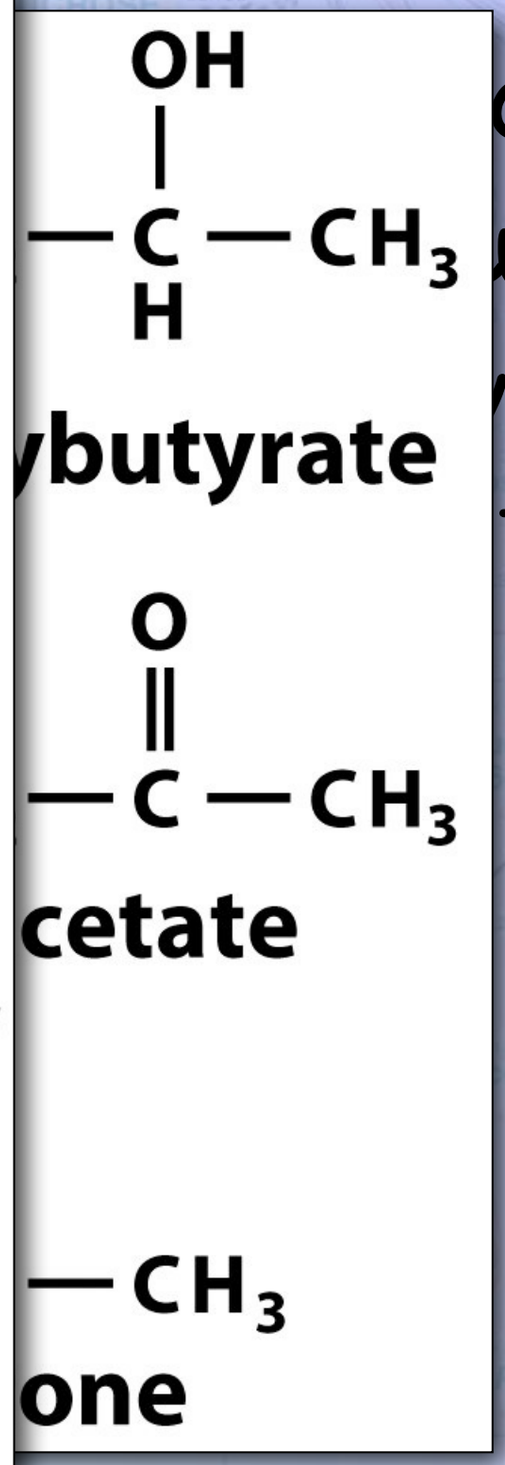
Ketone Bodies

Ketone bo…om
acetyl-Co…ulating
source of…
- Produce…term fasting



Ketone Bodies





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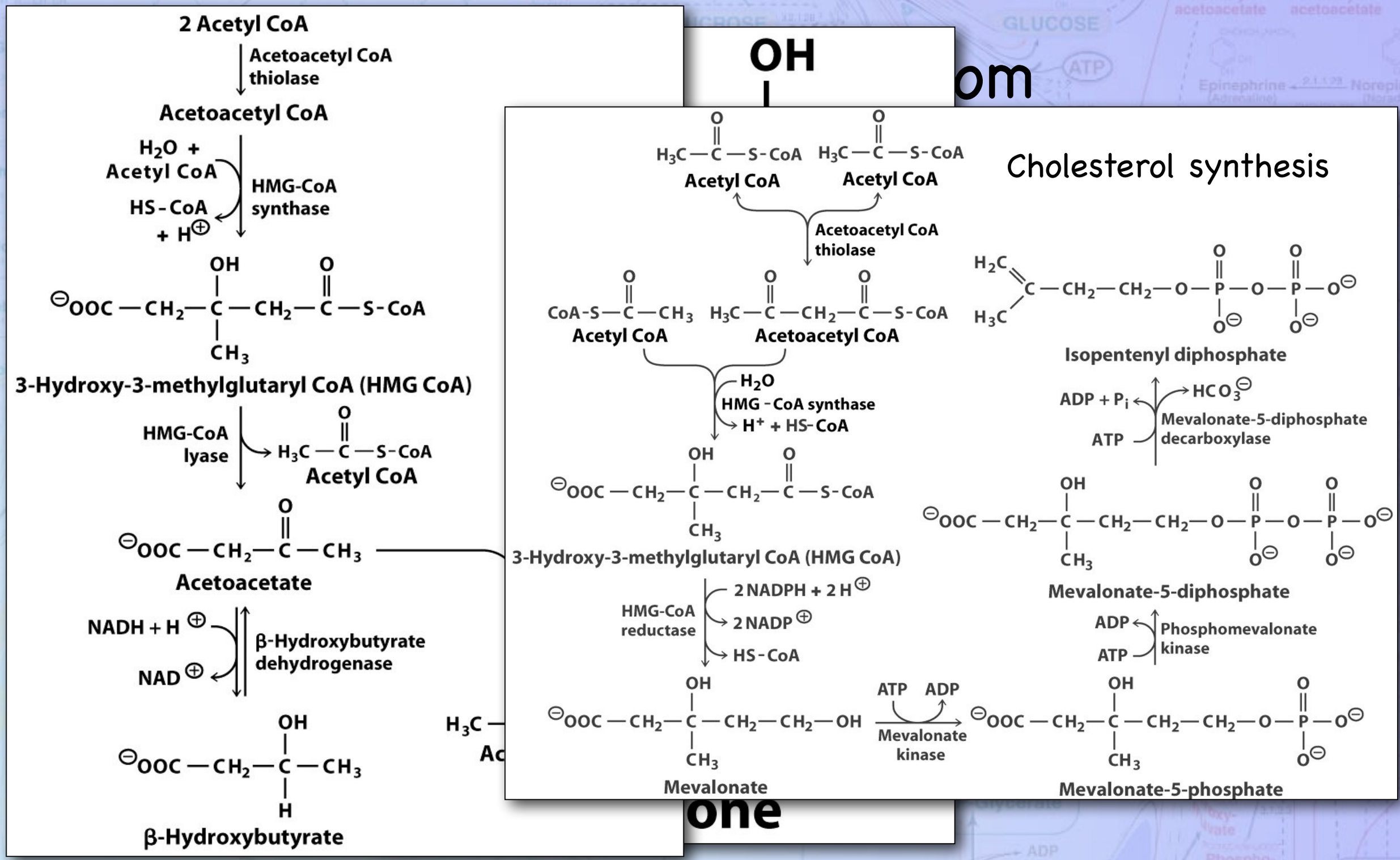
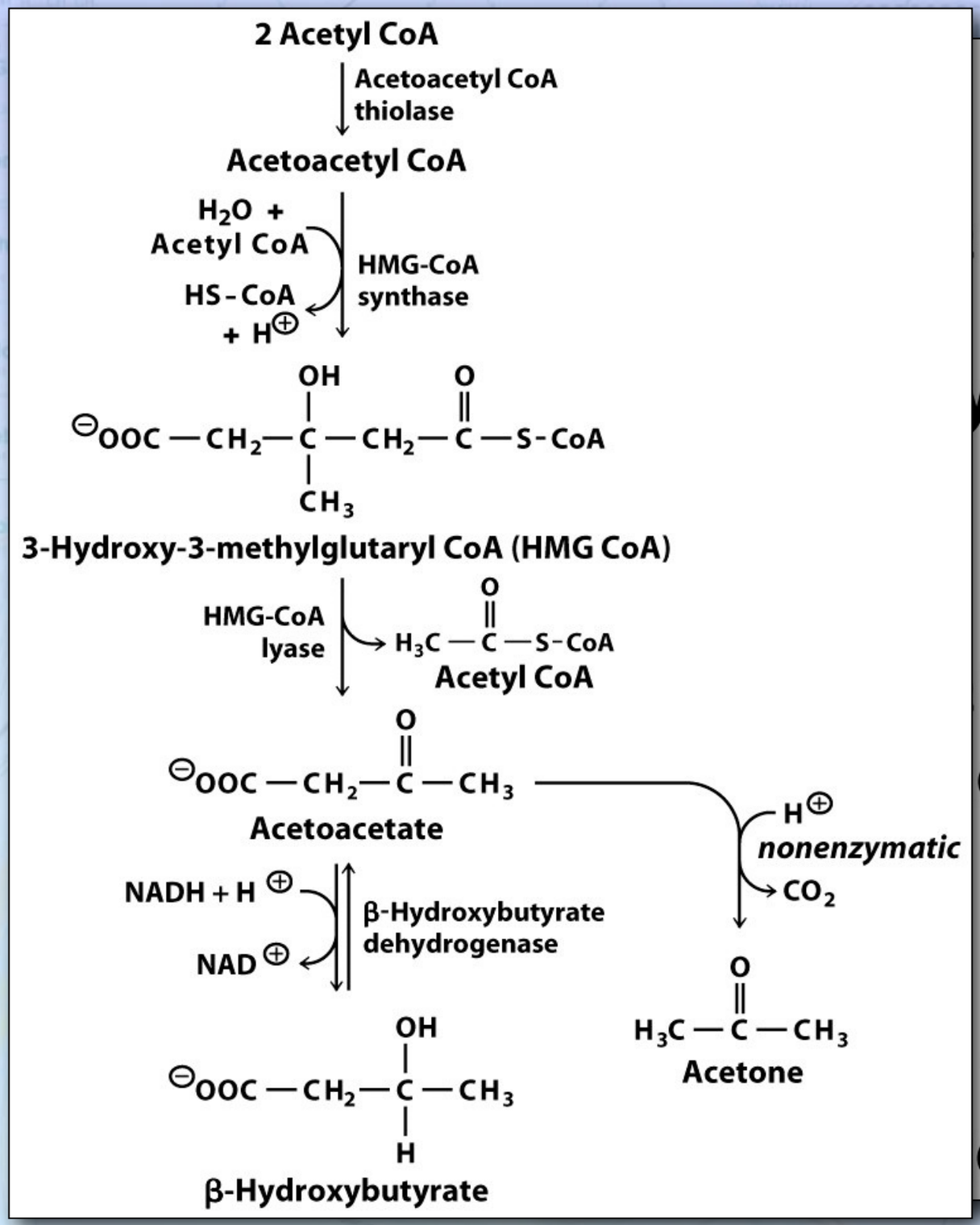
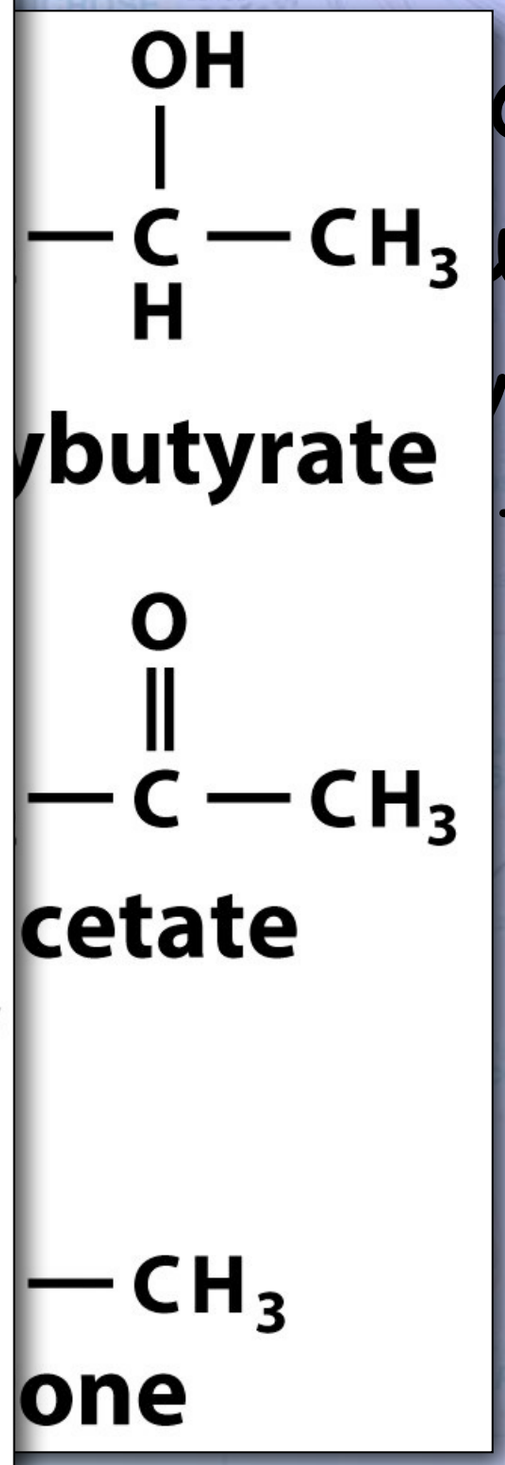
Ketone Bodies



Ketone Bodies





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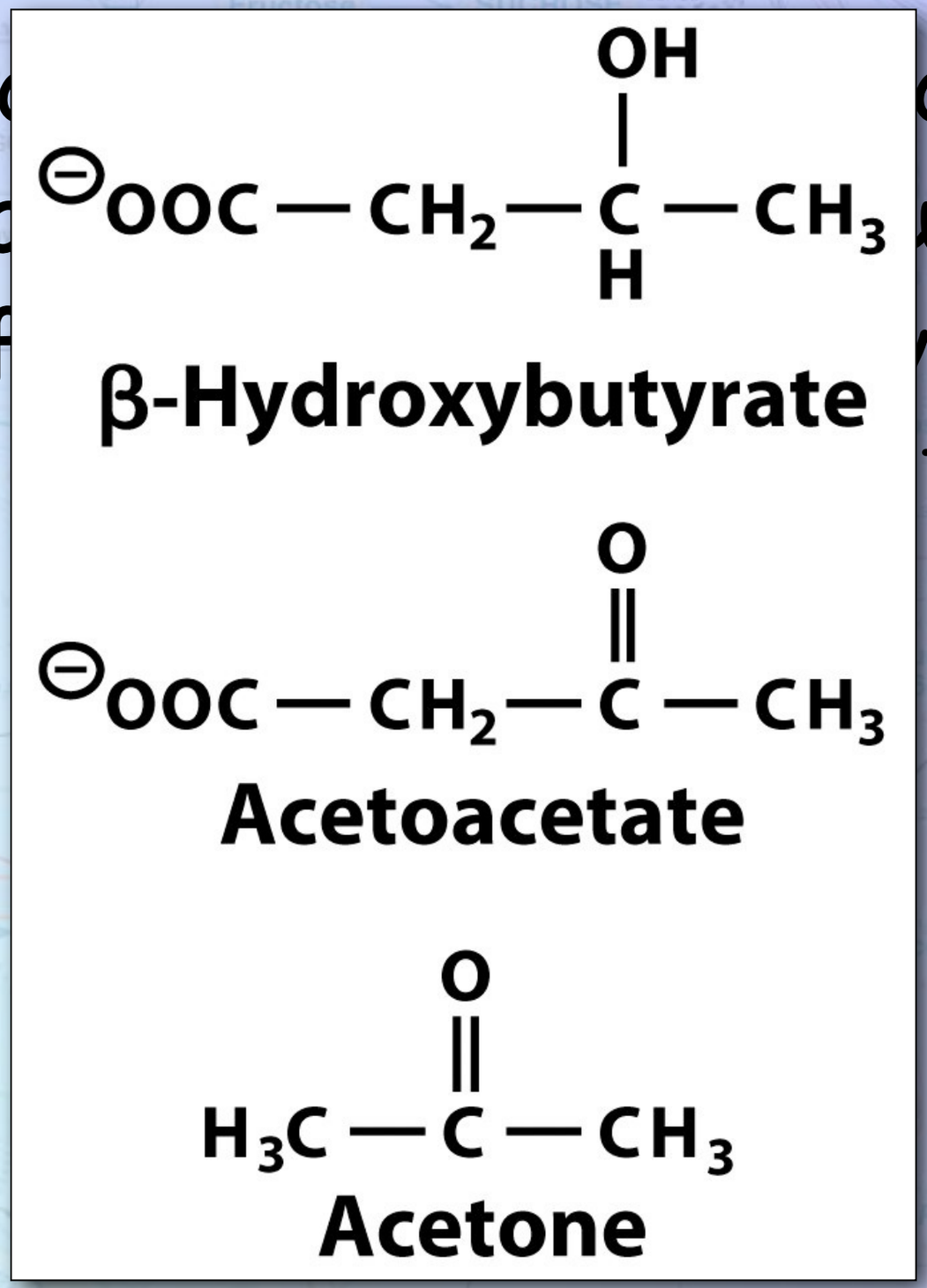
term fasting

Ketone Bodies

Ketone bo…om
acetyl-Co…ulating
source of…
- Produce…term fasting



Ketone Bodies

Ketone bo…om
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sou…
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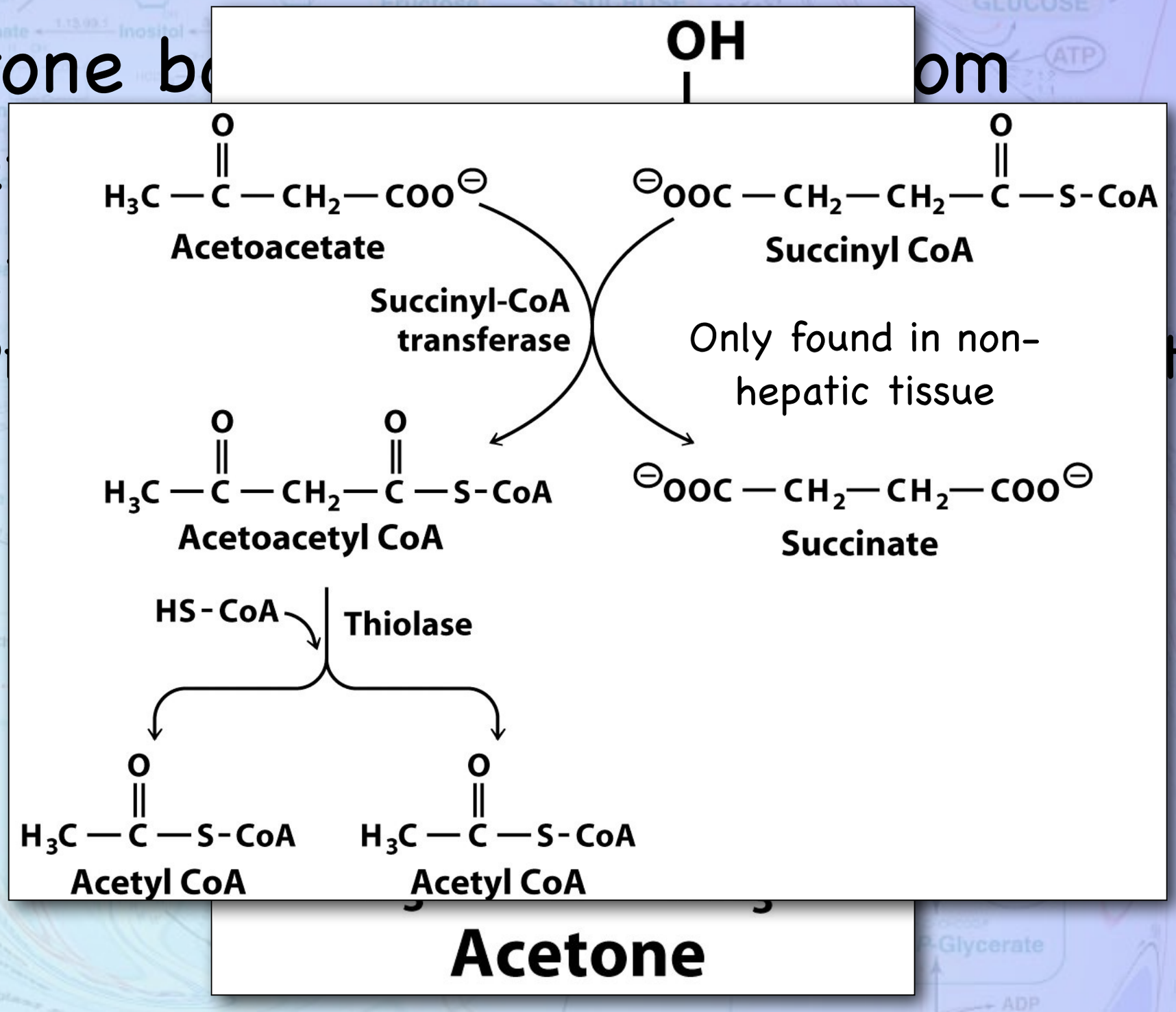

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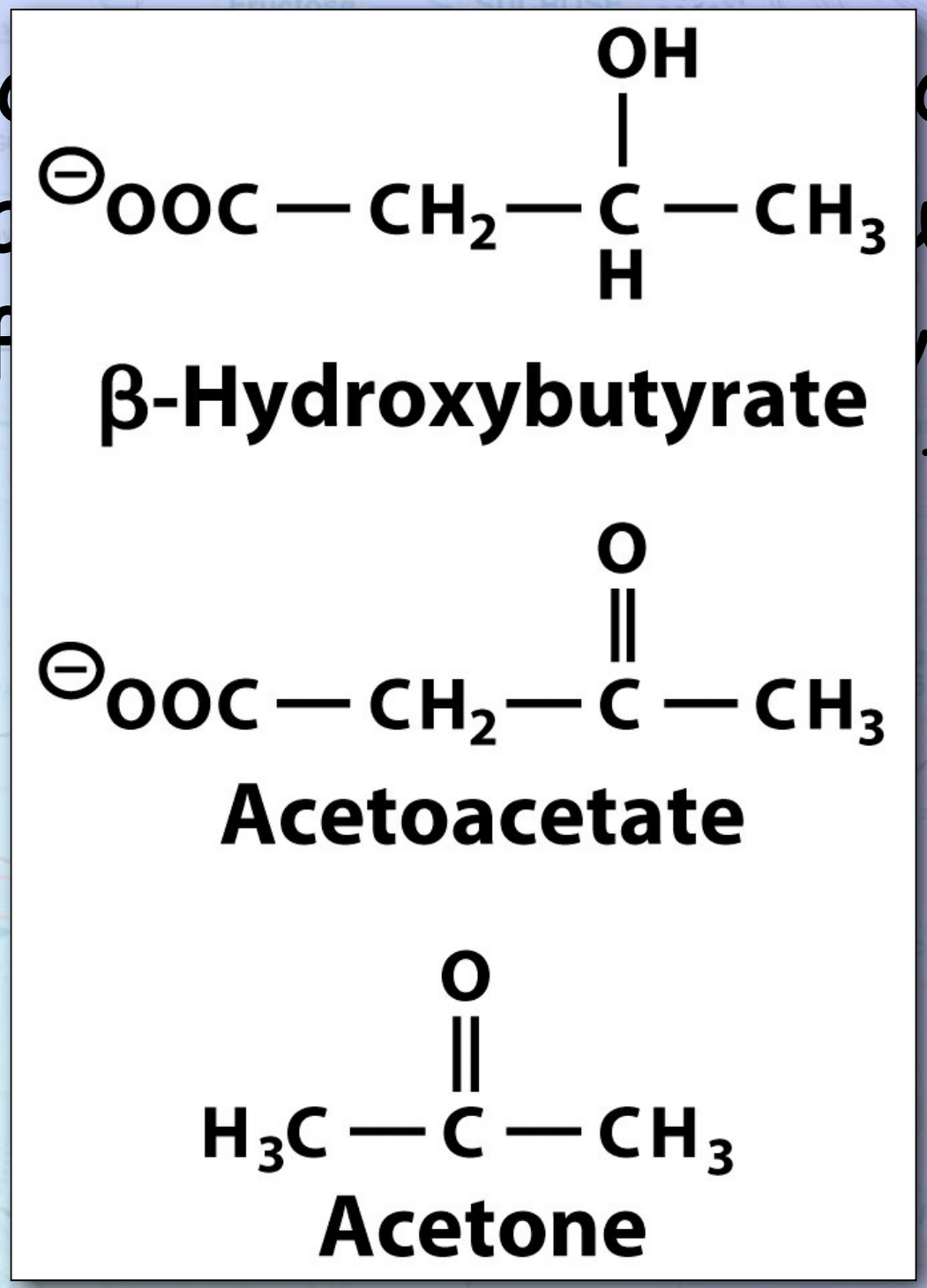

Lipid Metabolism

Lipid Metabolism

Question:

Draw a general pathway for converting carbohydrates to fatty acids in a liver cell, and indicate which processes occur in the cytosol and which occur in mitochondria.

Lipid Metabolism

Next Up

Lecture 10 - Part II, Amino acid metabolism (Moran et al., Chapter 17)