Biochemistry
Lipids metabolism

3rd lecture

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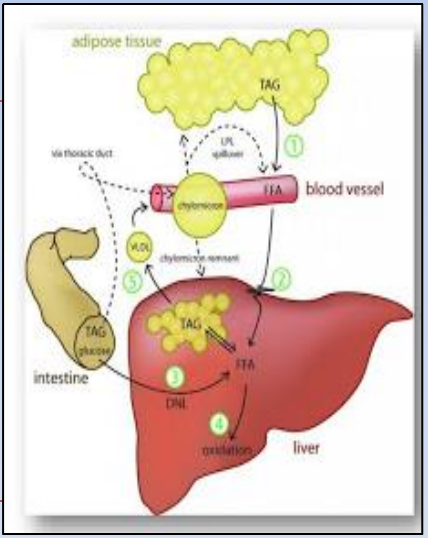
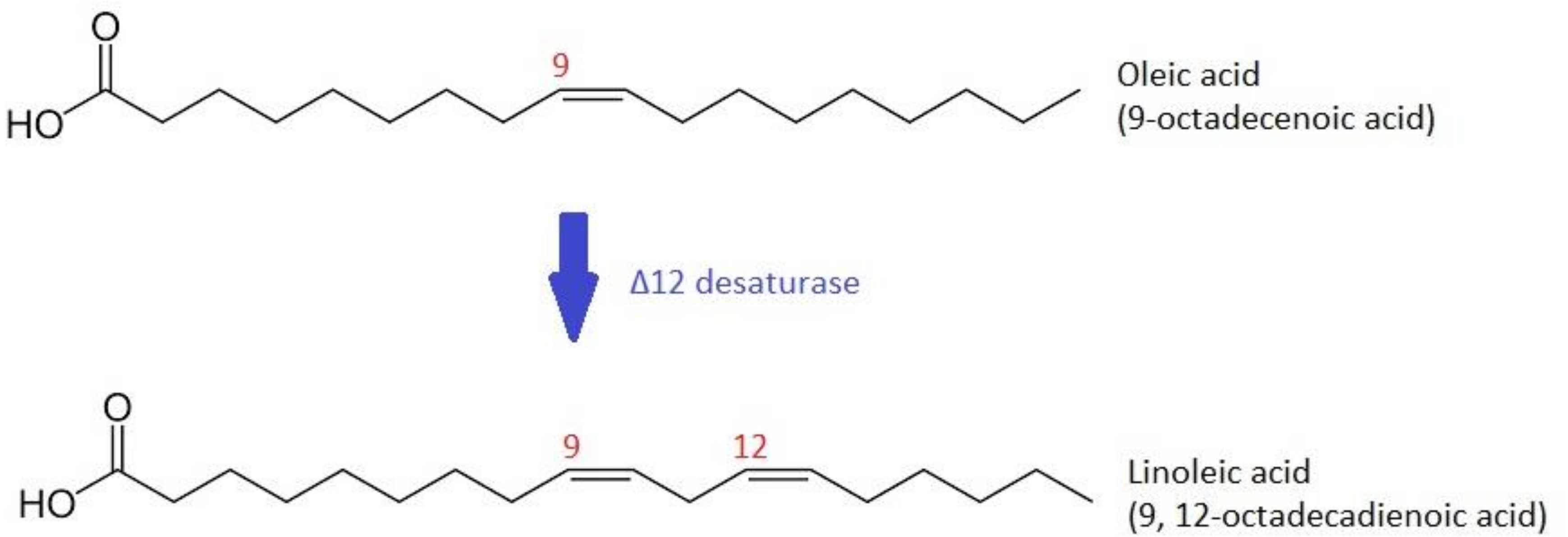


Out lines

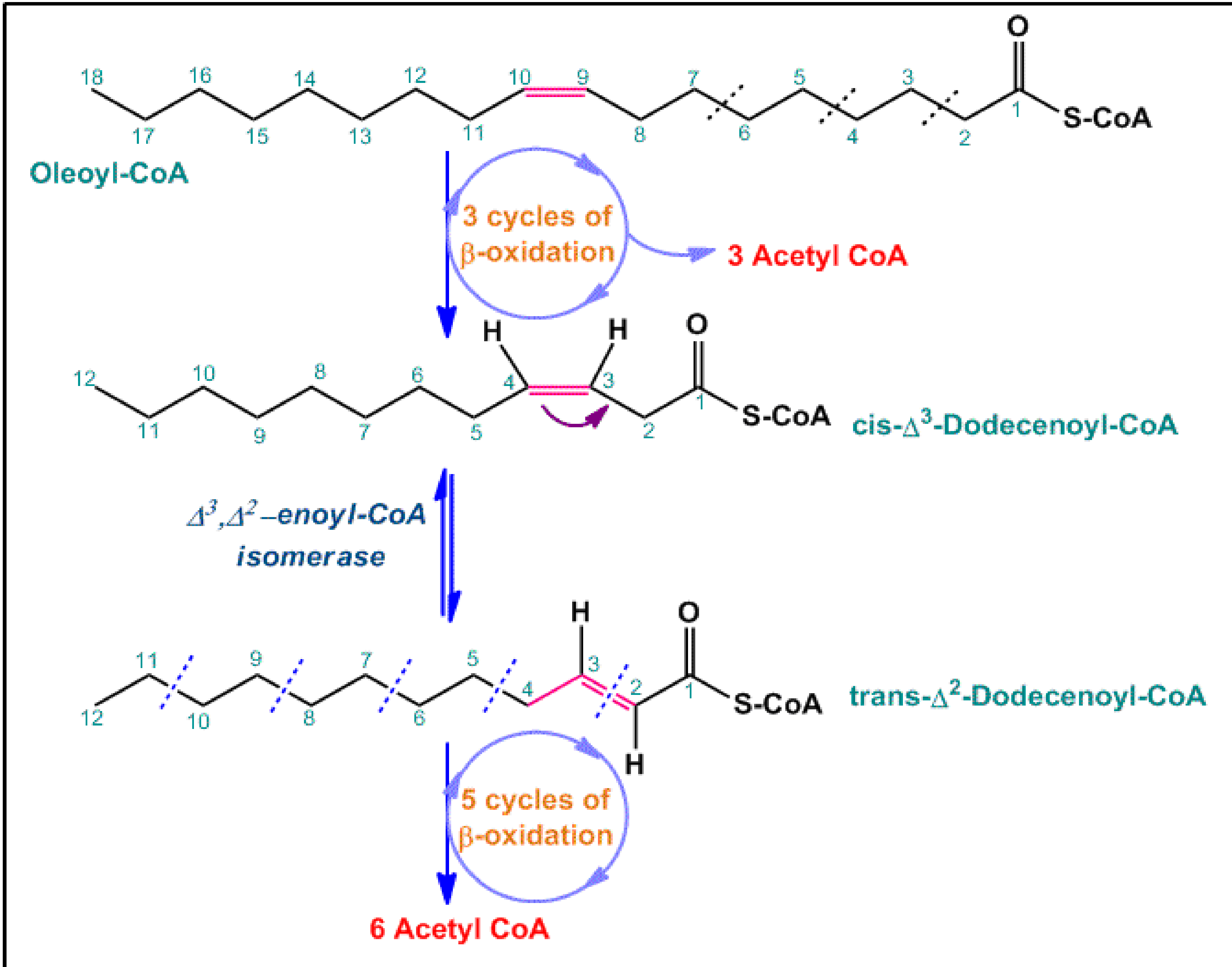
- Oxidation of unsaturated fatty acids
- Oxidation of odd- chain fatty acids
- Oxidation in peroxisome
- Summary of fatty acids oxidations
- Ketone bodied synthesis
- Regulation of ketogenesis.
- Cholesterol synthesis

Oxidation of Unsaturated Fatty Acids

Let us consider an example of monounsaturated fatty acid such as oleic acid and a polyunsaturated fatty acid such as linolenic acid. Oleic acid is an 18 carbon chain length fatty acid with a cis double bond present between the ninth and the tenth carbons. Linoleic acid is an 18 carbon chain length fatty acid with 2 cis double bonds between 9th and 10th carbons & 12th and 13th carbons.



- Just like the saturated fatty acids cross the mitochondrial membrane with the help of carnitine shuttle (For more details read Activation and Transportation of Fatty acids via Carnitine Shuttle), unsaturated fatty acids also reach the mitochondrial matrix as **fatty acyl-CoA.**
- The process of β-oxidation of oleic acid and linoleic acid by the enzymes present in the mitochondrial matrix is as shown below in the diagrams



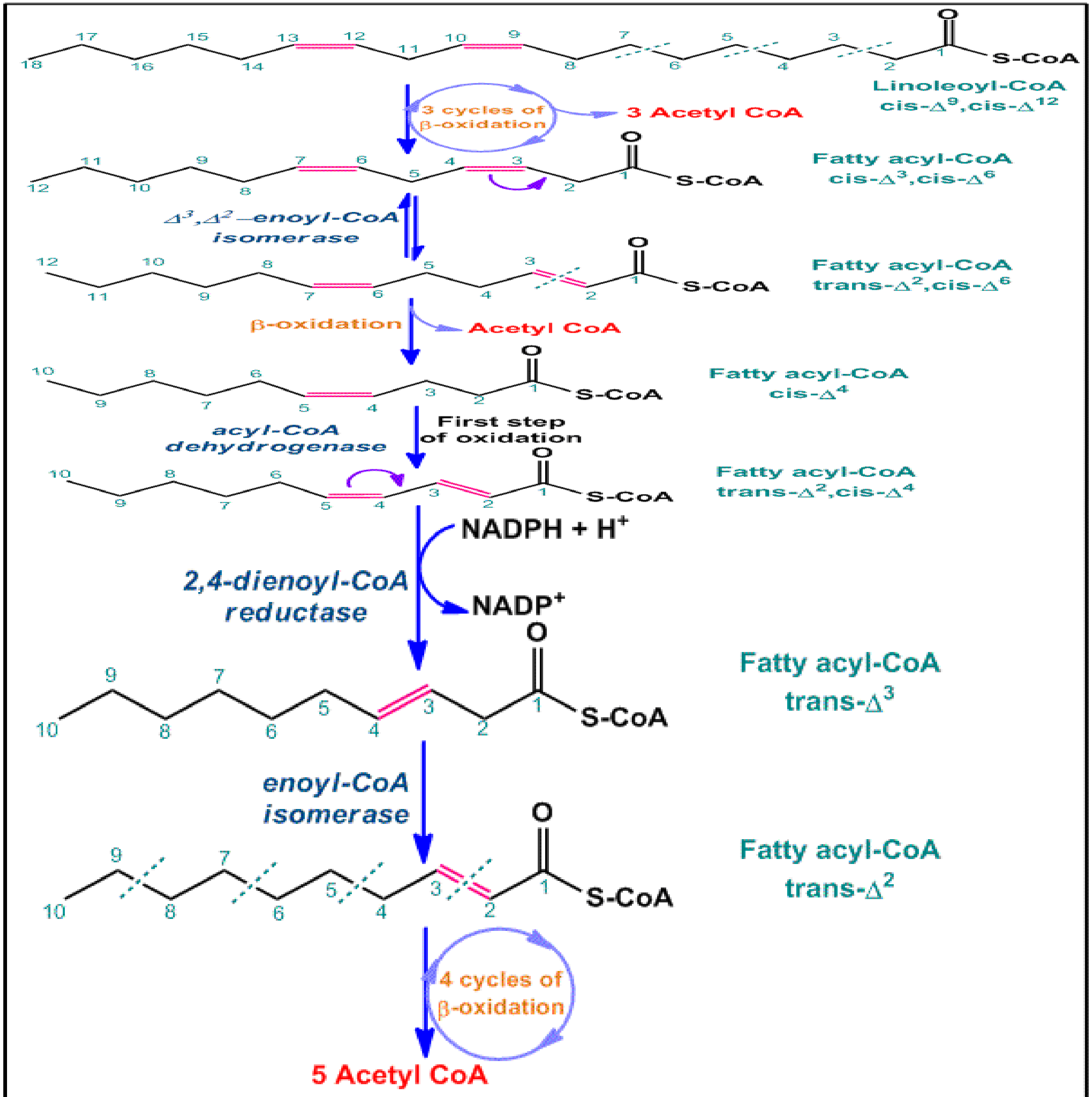
Oleoyl-CoA
S-CoA
3 cycles of β-oxidation
3 Acetyl CoA
cis-Δ3-Dodecenoyl-CoA
Δ3,Δ2–enoyl-CoA isomerase
trans-Δ2-Dodecenoyl-CoA
5 cycles of β-oxidation
6 Acetyl CoA

•**Oleoyl CoA** undergoes **three cycles of β-oxidation** like normal saturated fatty acids to yield **3 molecules of acetyl CoA** and results in the formation of 12-carbon fatty acyl-CoA with a **cis double bond** now between carbon 3 and 4. This product is known as **cis-Δ^3-Dodecenoyl-CoA**.

•The above product formed has **a cis double** bond and cannot further participate in β-oxidation. Thus by the action of ***Δ^3,Δ^2-enoyl-CoA isomerase***, **cis-Δ^3-Dodecenoyl-CoA** is converted to **trans-Δ^2-Dodecenoyl-CoA**. This is the significance of the ***isomerase*** enzyme in the β-oxidation of unsaturated fatty acids.

•**trans-Δ^2-Dodecenoyl-CoA** now is acted upon by the enzymes of **β-oxidation pathway** in five continuous cycles to yield another **6 molecules of acetyl CoA**.

•The **acetyl-CoA** molecules now enter the **Krebs's cycle**.



S-CoA
Linoleoyl-CoA
cis-Δ9,cis-Δ12
3 cycles of β-oxidation
3 Acetyl CoA
Fatty acyl-CoA
cis-Δ3,cis-Δ6
Δ3,Δ2 –enoyl-CoA isomerase
Fatty acyl-CoA
trans-Δ2,cis-Δ6
β-oxidation
Acetyl CoA
Fatty acyl-CoA
cis-Δ4
acyl-CoA dehydrogenase
First step of oxidation
Fatty acyl-CoA
trans-Δ2,cis-Δ4
NADPH + H+
NADP+
2,4-dienoyl-CoA reductase
Fatty acyl-CoA
trans-Δ3
enoyl-CoA isomerase
Fatty acyl-CoA
trans-Δ2
4 cycles of β-oxidation
5 Acetyl CoA

- **Linoleic acid** is an unsaturated fatty acid with **two cis** double bonds. Like saturated fatty acids the polysaturated fatty acid undergoes **three cycles of β-oxidation** to yield **three molecules of acetyl CoA** along with a 12 carbon chain fatty acyl-CoA with cis double bonds at position 3 and 6 **(cis-Δ^3,cis-Δ^6).**
- Since the mitochondrial enzymes cannot break down cis double bonds, ***Δ^3,Δ^2- enoyl-CoA isomerase*** converts it to **(trans-Δ^2,cis-Δ^6) fatty acyl-CoA**. The latter product now undergoes **one more cycle of β-oxidation** to yield the **fourth molecule of acetyl CoA** and the remaining product left behind is **cis-Δ^4 fatty acyl-CoA**.

- By the action of ***acyl-CoA dehydrogenase***, the first step of β-oxidation is achieved, resulting in formation of a double bond at position 2 forming the product **(trans-Δ^2,cis-Δ^4) fatty acyl-CoA**. The newly formed product is now acted upon by the enzyme ***2,4-dienoyl CoA-reductase*** to form **trans-Δ^3 fatty acyl-CoA** which on further action by ***enoyl-CoA isomerase*** gives **trans-Δ^2 fatty acyl-CoA**.

trans-Δ^2 fatty acyl CoA now undergoes **four cycles of β-oxidation** to yield another **five molecules of acetyl CoA**.

- The **acetyl-CoA** molecules now enter the **Kreb's cycle**.

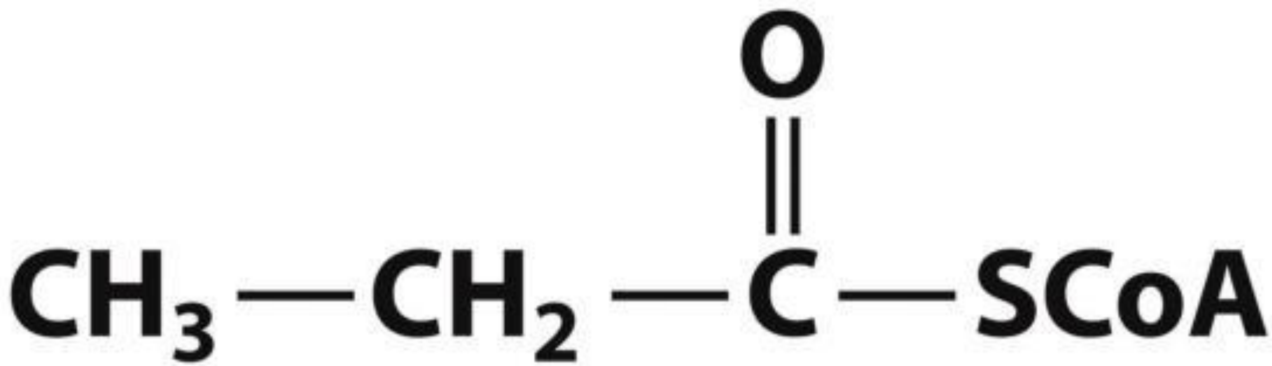
Which type of fatty acid produce more energy ?

A. Saturated fatty acids
B. Unsaturated fatty acids

Beta-oxidation of unsaturated fatty acids

- Unsaturated FA yield a bit less energy than saturated FA because they are already partially oxidized
- Less $FADH_2$ is produced

Oxidation of odd-chain fatty acids yields propionyl-CoA.



Propionyl-CoA

Oxidation of odd-chain fatty acids yields propionyl-CoA

Most fatty acids have an even number of carbon atoms (this is because they are synthesized by the **addition of two-carbon acetyl units**, as we will see later in this chapter). However, some **plant and bacterial fatty acids that make their way into the human system have an odd number of carbon atoms**. *The final round of β oxidation of these molecules leaves a three-carbon fragment, propionyl-CoA, rather than the usual acetyl-CoA.*

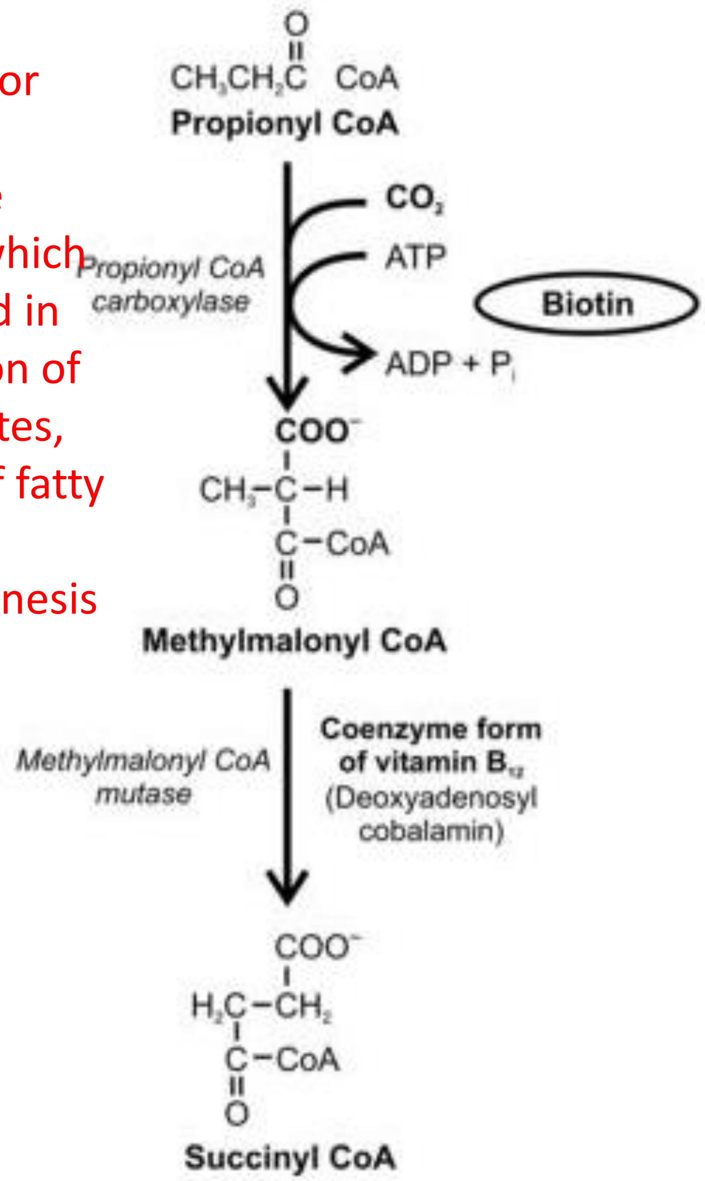
Propionyl-CoA

This intermediate can be further metabolized by the sequence of steps outlined in **Figure** **At first, this pathway seems longer than necessary**. For example, **adding a carbon to C3** of the propionyl group would immediately **generate succinyl-CoA**. However, such a reaction is **not chemically favored**, **because C3 is too far from the electron-delocalizing effects of the CoA thioester**. Consequently, propionyl-CoA carboxylase must add a carbon to C2, and then methylmalonyl-CoA mutase must rearrange the carbon skeleton to produce succinyl-CoA. Note that succinyl-CoA is not the end point of the pathway. Because it is a citric acid cycle intermediate, it acts catalytically and is not consumed by the cycle. ***The complete catabolism of the carbons derived from propionyl-CoA requires that the succinyl-CoA be converted to pyruvate and then to acetyl-CoA, which enters the citric acid cycle as a substrate***.

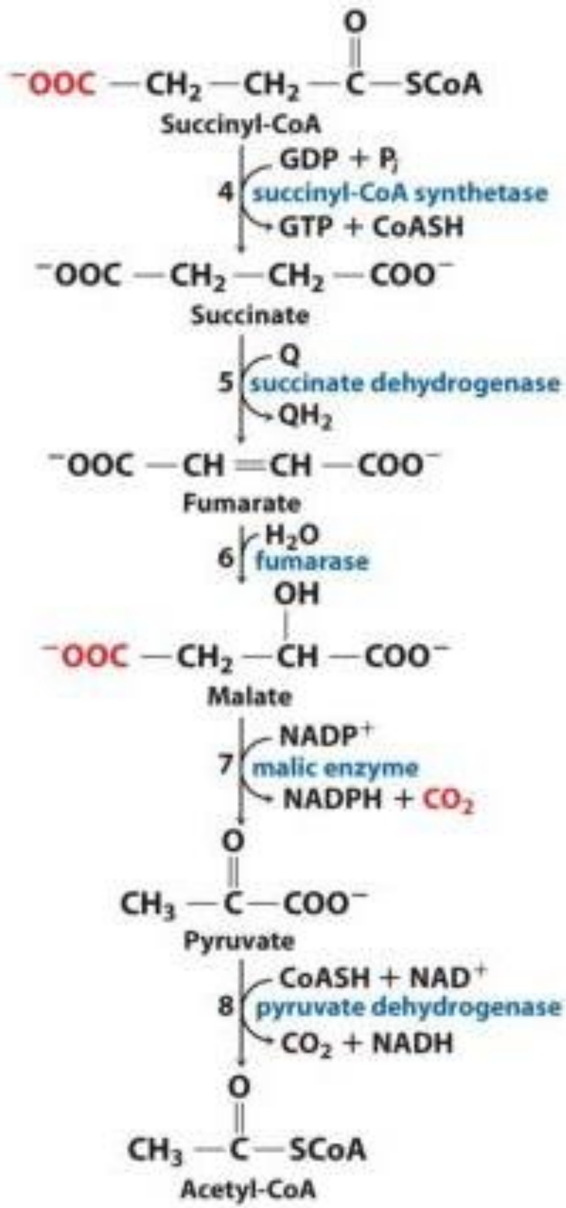
Beta-oxidation of odd-chain fatty acids

- **Odd-chain FA** degradation yields acetyl CoAs and one **propionyl CoA**
- Propionyl CoA is metabolized by carboxylation to methylmalonyl CoA (carboxylase is a biotin enzyme)
- Methyl carbon is moved within the molecule by methylmalonyl CoA mutase (one of only two Vitamin B_{12} cofactor enzymes) to form **succinyl CoA**

Biotin is a coenzyme for five carboxylase **enzymes**, which are involved in the digestion of carbohydrates, synthesis of fatty acids, and gluconeogenesis



Breakdown of Propionyl-CoA



4–6. *Succinyl-CoA, a citric acid cycle intermediate, is converted to malate by reactions 5–7 of the citric acid cycle*

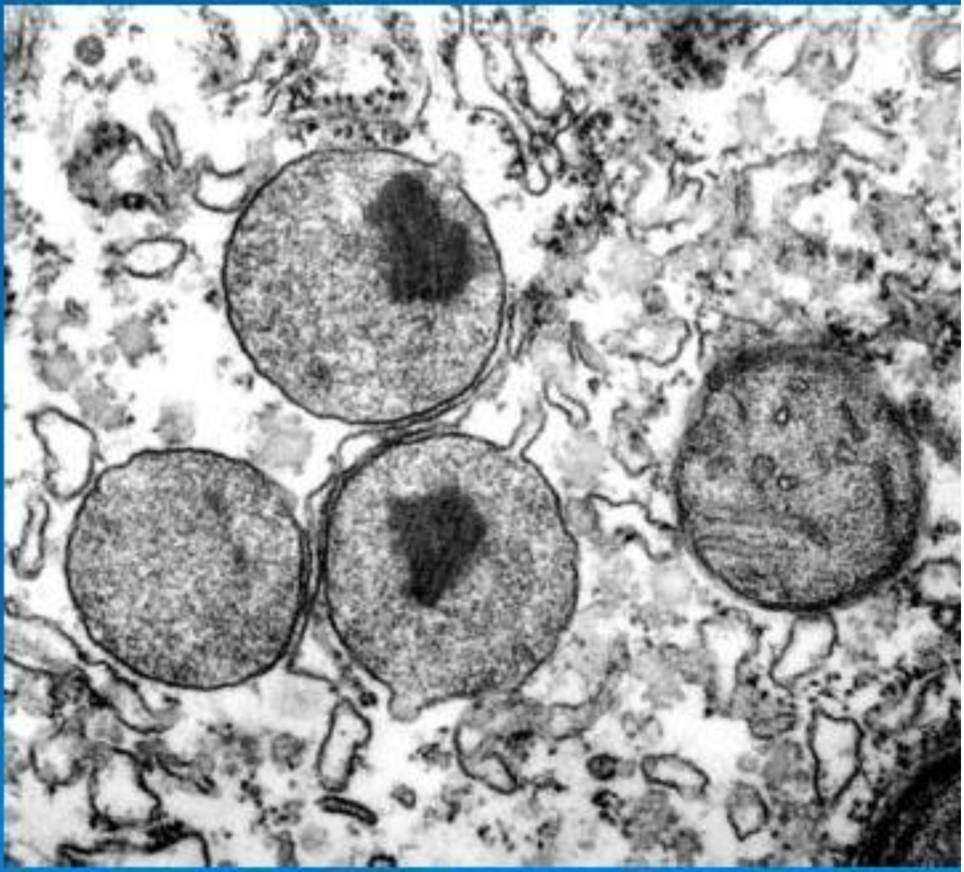
7. *After being exported from the mitochondria, malate is decarboxylated by malic enzyme to produce pyruvate in the cytosol.*

8. *Pyruvate, imported back into the mitochondria, can then be converted to acetyl-CoA by the pyruvate dehydrogenase complex.*

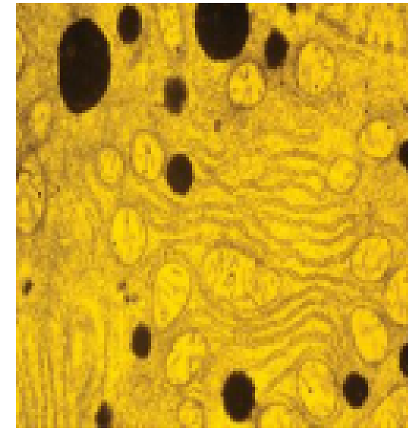
Some fatty acid oxidation occurs in peroxisomes.

- Peroxisomes are organelles that are bound by a single membrane.

- In animals, β oxidation of FAs occurs both in peroxisome and mitochondrion
- Peroxisomal β oxidation shortens very long chain FAs (> 22 C atoms) in order to facilitate mitochondrial β oxidation
- In yeast and plants, FA oxidation occurs exclusively in the peroxisomes and glyoxysomes

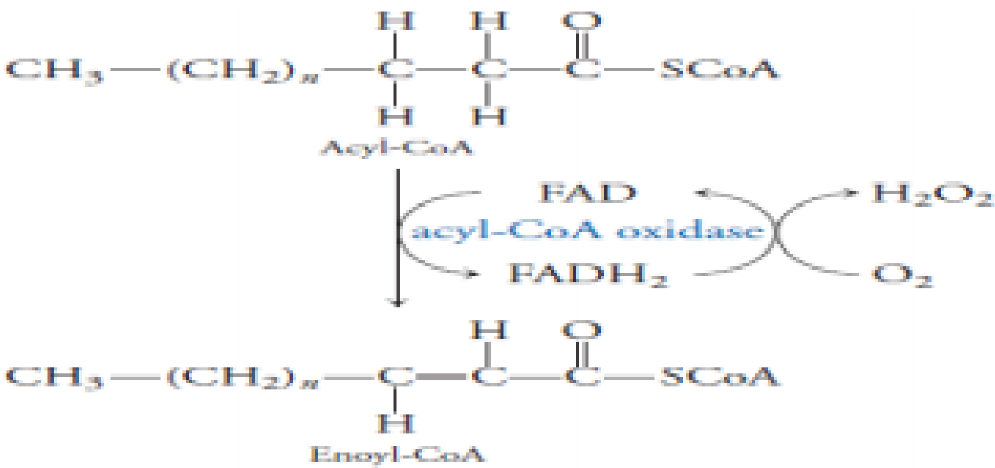


Some fatty acid oxidation occurs in peroxisomes



The majority of a mammalian cell's fatty acid oxidation occurs in mitochondria, but a small percentage is carried out in organelles known as **peroxisomes (Fig.14).** In plants, all fatty acid oxidation occurs in peroxisomes and glyoxysomes. Peroxisomes are enclosed by a single membrane and contain a variety of degradative and biosynthetic enzymes. The peroxisomal b oxidation pathway differs from the mitochondrial pathway in the first step. An **acyl-CoA oxidase** catalyzes the reaction (in mitochondria **is catalyzed by an acyl-CoA dehydrogenase**).

Figure 14. Peroxisomes. Nearly all eukaryotic cells contain these single membrane- bound organelles (dark structures), which are similar to plant glyoxysome.



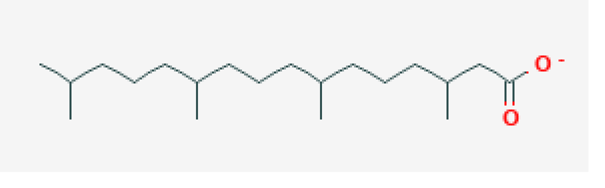
The enoyl-CoA product of the reaction is identical to the product of the mitochondrial acyl-CoA dehydrogenase reaction but the electrons removed from the acyl-CoA are transferred not to ubiquinone but directly to molecular oxygen to produce hydrogen peroxide, H_2O_2. This reaction product, which gives the peroxisome its name, is subsequently broken down by the peroxisomal enzyme catalase:

$$2\,H_2O_2 \rightarrow 2\,H_2O + O_2$$

Functions of peroxisome

Because the peroxisomal oxidation enzymes are specific for very-long-chain fatty acids (such as those containing over 20 carbons) and bind short-chain fatty acids with low affinity, ***the peroxisome serves as a chain-shortening system***. The partially degraded fatty acyl-CoAs then make their way to the mitochondria for complete oxidation.

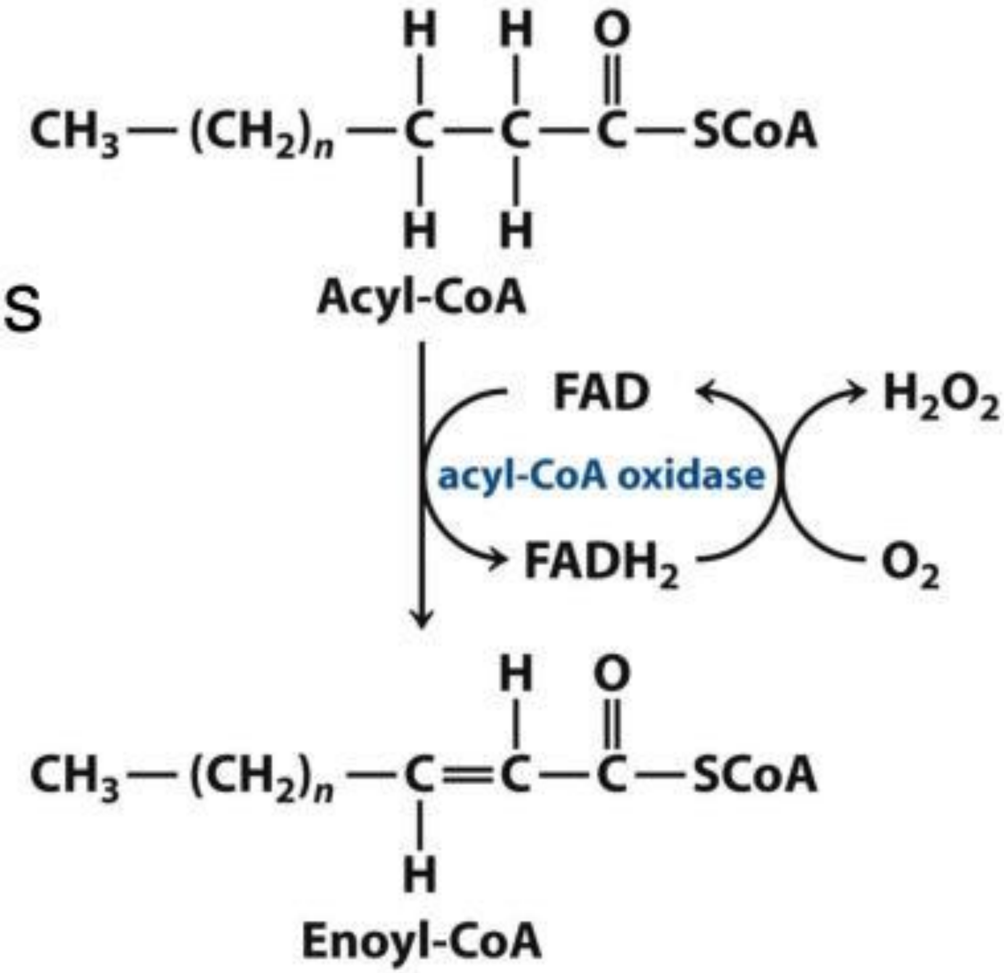
The peroxisome is also responsible for **degrading some branched-chain fatty acids**, which are **not recognized by the mitochondrial enzymes**. One such nonstandard fatty acid is phytanate, which is derived from the side chain of chlorophyll molecules and is present in all plant-containing diets. Phytanate must be degraded by peroxisoma lenzymes because the methyl group at C3 prevents dehydrogenation by 3- hydroxyacyl-CoA dehydrogenase (step 3 of the standard β oxidation pathway).



$C_{20}H_{39}O_2^-$

Fatty acid oxidation in peroxisomes differs from that in mitochondria.

- Step 1: Electrons are transferred from $FADH_2$ to H_2O_2 instead of ubiquinone



SUMMARY (Fatty Acid Oxidation)

- In the process of b oxidation, a series of four enzymatic reactions degrades a fatty acyl-CoA two carbons at a time, producing one QH2, one NADH, and one acetyl-CoA, which can be further oxidized by the citric acid cycle. Reoxidation of the reduced cofactors generates considerable ATP.

- Oxidation of unsaturated and odd-chain fatty acids requires additional enzymes. Very-long-chain and branched fatty acids are oxidized in peroxisomes.

- Additional enzymes are required to break down unsaturated fatty acids.
- Fatty acids with an odd number of carbons yield propionyl-CoA that is ultimately converted to acetyl-CoA.
- Peroxisomes oxidize long-chain and branched fatty acids, producing H_2O_2.