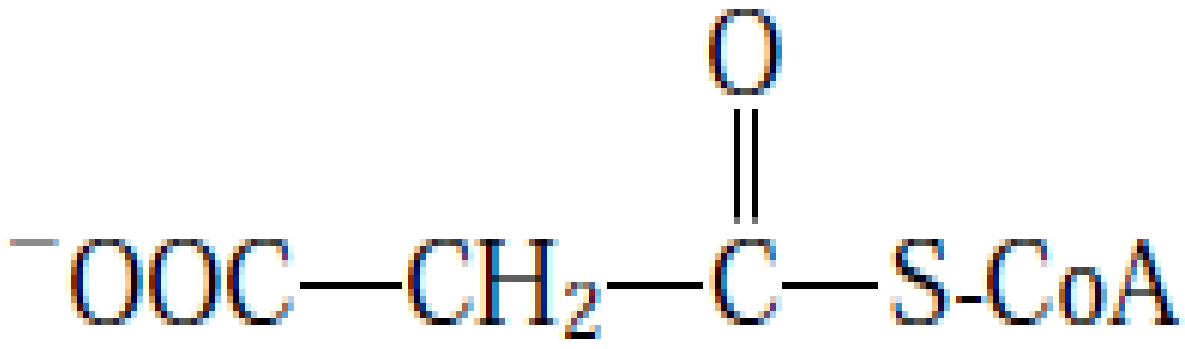
LIPID METABOLISM-3

Regulation of Fatty Acid Oxidation

1. Carnitine shuttle by which fatty acyl groups are carried from cytosolic fatty acyl–CoA into the mitochondrial matrix is rate limiting for fatty acid oxidation and is an important point of regulation.

2. Malonyl-CoA, the first intermediate in the cytosolic biosynthesis of long-chain fatty acids from acetyl-CoA increases in concentration whenever the body is well supplied with carbohydrate; excess glucose that cannot be oxidized or stored as glycogen is converted in the cytosol into fatty acids for storage as triacylglycerol.

The inhibition of **CAT I** by **malonyl-CoA** ensures that the oxidation of fatty acids is inhibited whenever the liver is actively making triacylglycerols from excess glucose.



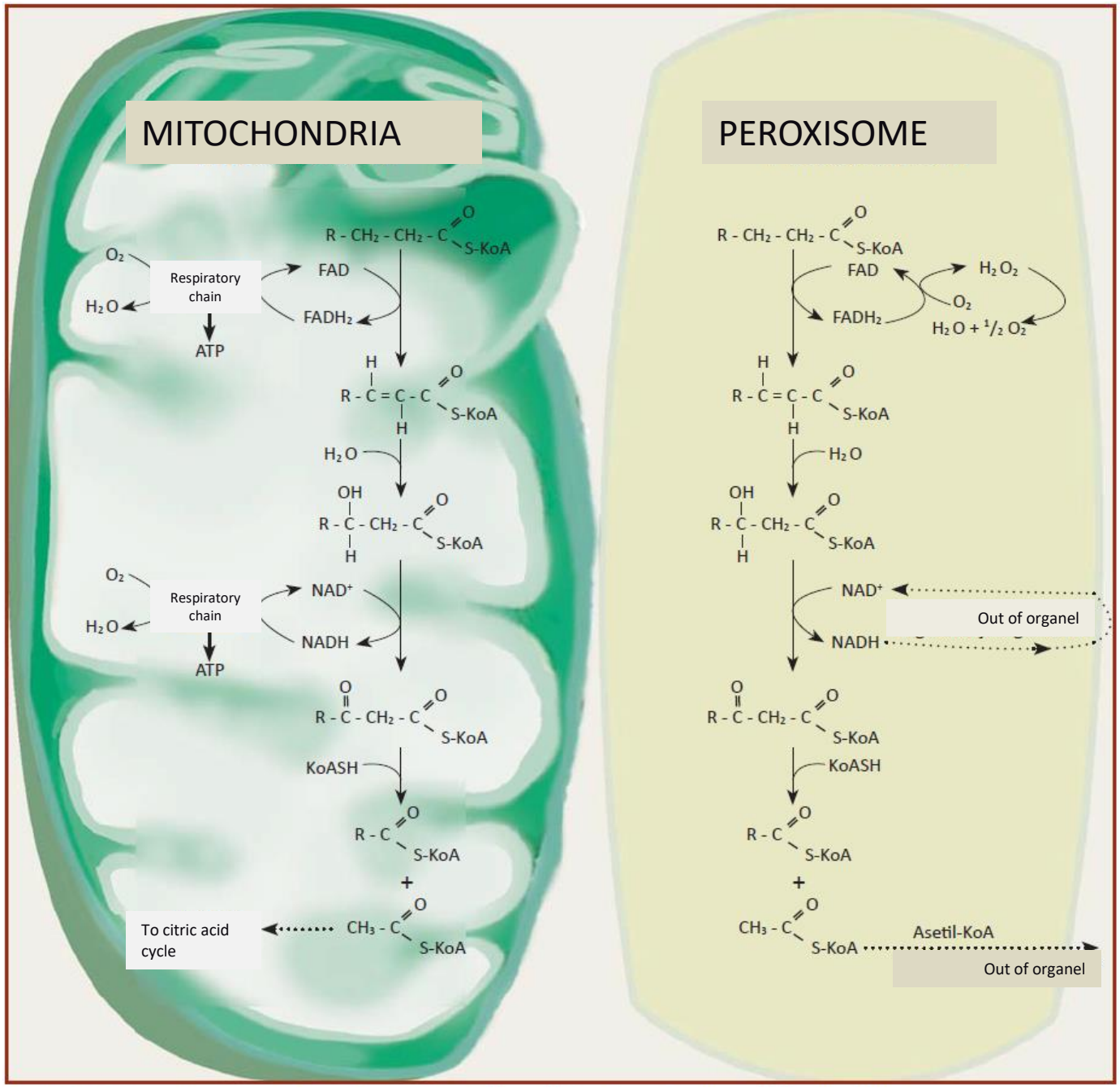
Malonyl-CoA

Two of the enzymes of β-oxidation are also regulated by metabolites that signal energy sufficiency.

3. When the [NADH]/[NAD^+] ratio is high, β-hydroxyacyl-CoA dehydrogenase is inhibited;

4. When acetyl-CoA concentration is high, thiolase is inhibited.

5. During periods of vigorous muscle contraction or during fasting, the fall in [ATP] and the rise in [AMP] activate the AMP-activated protein kinase (AMPK). AMPK phosphorylates several target enzymes, including acetyl-CoA carboxylase (ACC), which catalyzes malonyl-CoA synthesis. Phosphorylation and inhibition of ACC lowers the concentration of malonyl-CoA, relieving the inhibition of acyl–carnitine transport into mitochondria and allowing oxidation to replenish the supply of ATP.



Comparison of mitochondrial and peroxisomal beta-oxidation

- Another important difference between mitochondrial and peroxisomal oxidation in mammals is in the specificity for fatty acyl–CoAs; the peroxisomal system is much more active on very-long-chain fatty acids such as hexacosanoic acid (26:0) and on branched chain fatty acids such as phytanic acid and pristanic acid.

- These less-common fatty acids are obtained in the diet from dairy products, the fat of ruminant animals, meat, and fish.
- Their catabolism in the peroxisome involves several auxiliary enzymes unique to this organelle.

- The inability to oxidize these compounds is responsible for several serious human diseases.
- Individuals with **Zellweger syndrome** are unable to make peroxisomes and therefore lack all the metabolism unique to that organelle.

- In **X-linked adrenoleukodystrophy (XALD)**, peroxisomes fail to oxidize very-long-chain fatty acids, apparently for lack of a functional transporter for these fatty acids in the peroxisomal membrane.

- Both defects lead to accumulation in the blood of very-long-chain fatty acids, especially 26:0.
- XALD affects young boys before the age of 10 years, causing loss of vision, behavioral disturbances, and death within a few years.

- In mammals, high concentrations of fats in the diet result in increased synthesis of the enzymes of peroxisomal oxidation in the liver.

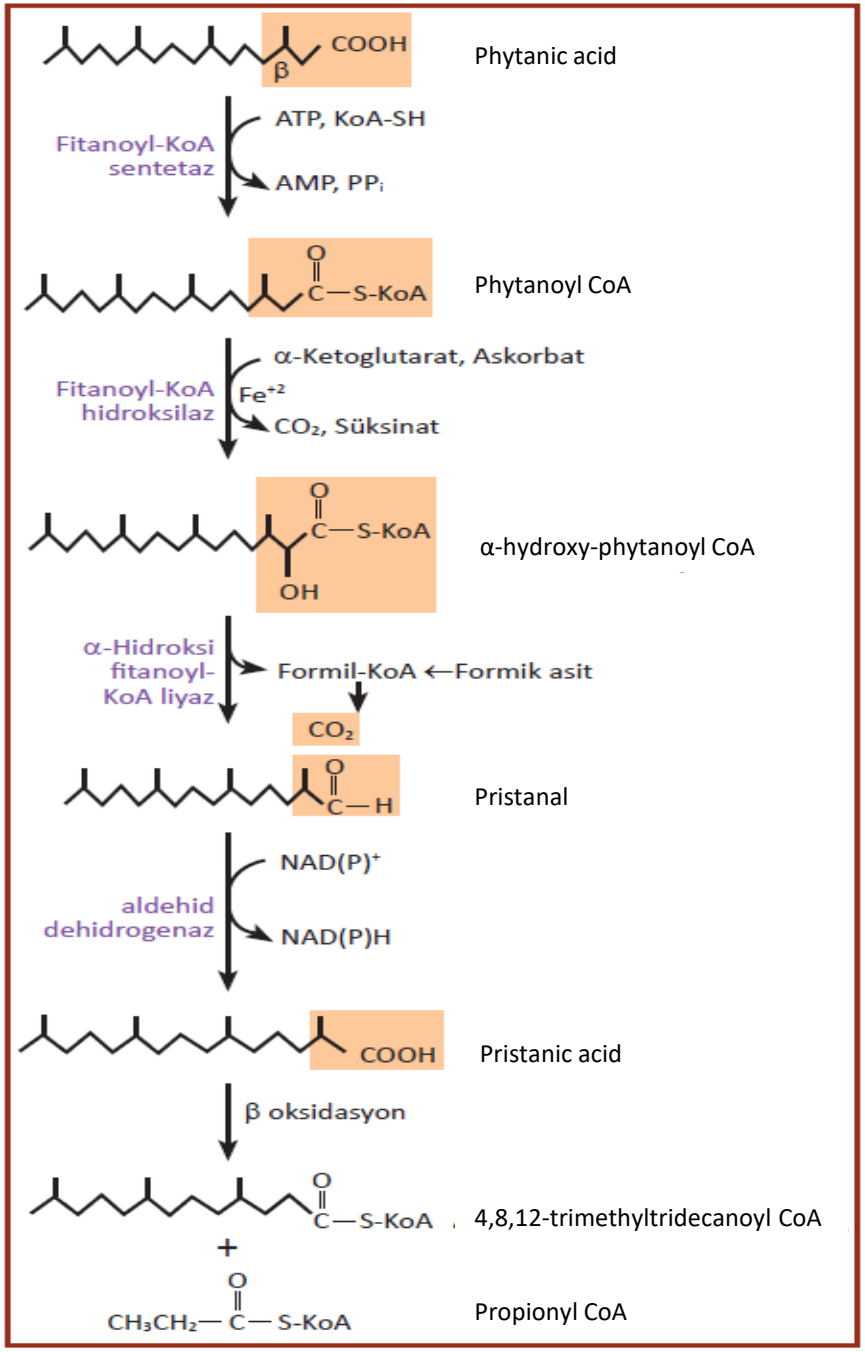
- Liver peroxisomes do not contain the enzymes of the citric acid cycle and cannot catalyze the oxidation of acetyl-CoA to CO_2. Instead, long-chain or branched fatty acids are catabolized to shorter-chain products, such as hexanoyl-CoA, which are exported to mitochondria and completely oxidized.

α-oxidation

- The presence of a methyl group on the β-carbon of a fatty acid makes β-oxidation impossible, and these branched fatty acids are catabolized in peroxisomes by ***α*-oxidation**.

- In the oxidation of phytanic acid, for example, phytanoyl-CoA is hydroxylated on its α-carbon, in a reaction that involves molecular oxygen; decarboxylated to form an aldehyde one carbon shorter; and then oxidized to the corresponding carboxylic acid, which now has no substituent on the β-carbon and can be oxidized further by β -oxidation.

α-oxidation of phytanic acid



- **Refsum disease**, resulting from a genetic defect in phytanoyl-CoA hydroxylase, leads to very high blood levels of phytanic acid and severe neurological problems, including blindness and deafness.

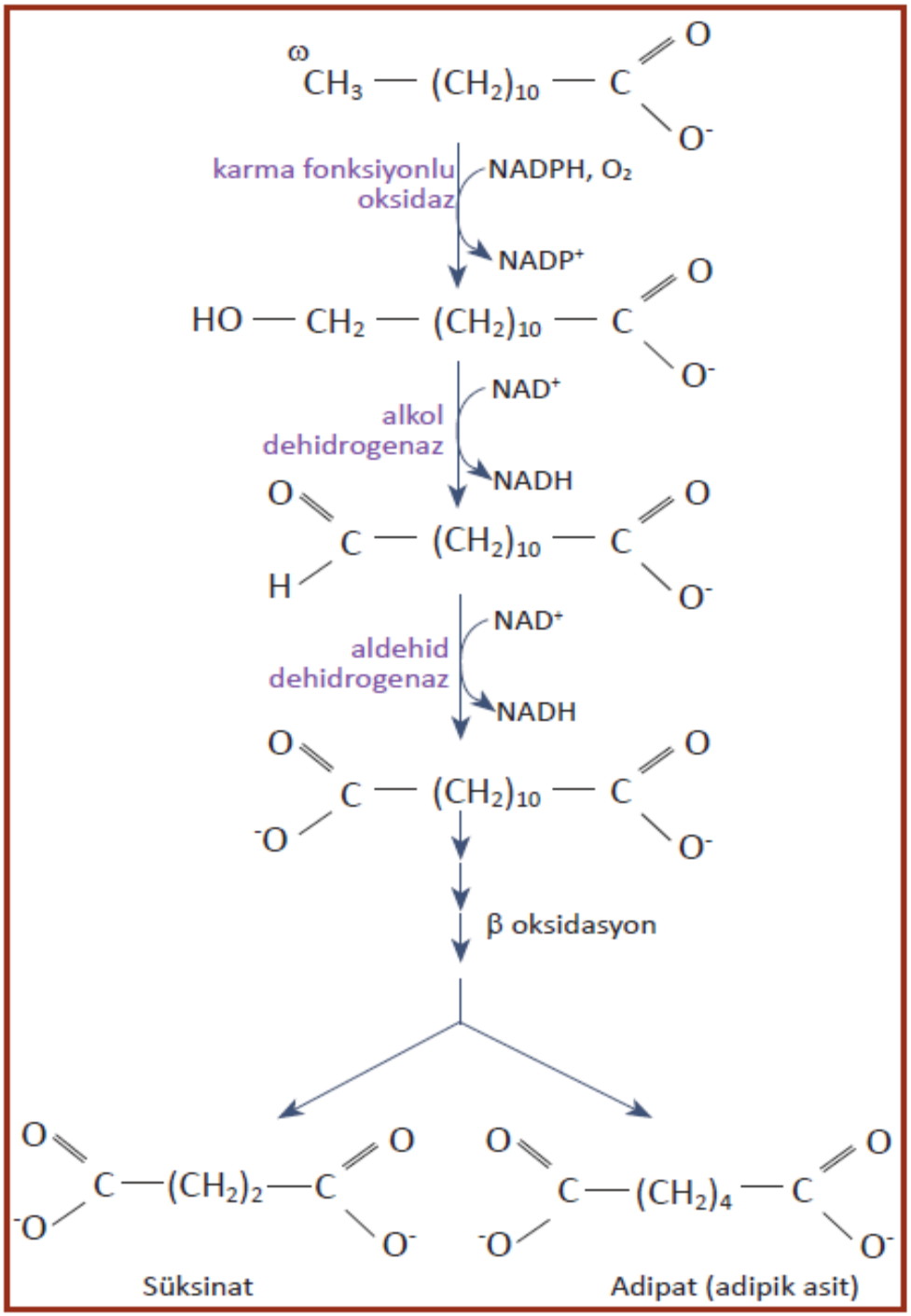
Omega(ω)-oxidation

- The enzymes unique to ***ω*-oxidation** are located in the endoplasmic reticulum of liver and kidney, and the preferred substrates are fatty acids of 10 or 12 carbon atoms.
- In mammals ω-oxidation is normally a minor pathway for fatty acid degradation, but when β-oxidation is defective (because of mutation or a carnitine deficiency, for example) it becomes more important.

- The first step introduces a hydroxyl group onto the ω-carbon catalyzed by a **mixed-function oxidase**.
- Two more enzymes act on the ω-carbon: **alcohol dehydrogenase** oxidizes the hydroxyl group to an aldehyde, and **aldehyde dehydrogenase** oxidizes the aldehyde group to a carboxylic acid, producing a fatty acid with a carboxyl group at each end.

- At this point, either end can be attached to coenzyme A, and the molecule can enter the mitochondrion and undergo β-oxidation by the normal route.
- In each pass through the β-oxidation pathway, the “double-ended” fatty acid yields dicarboxylic acids such as succinic acid, which can enter the citric acid cycle, and adipic acid.

Omega(ω)-oxidation



Transcription Factors Turn on the Synthesis of Proteins for Lipid Catabolism

- In addition to the various short-term regulatory mechanisms that modulate the activity of existing enzymes, transcriptional regulation can change the number of molecules of the enzymes of fatty acid oxidation on a longer time scale, minutes to hours.

- The **PPAR** family of nuclear receptors are transcription factors that affect many metabolic processes in response to a variety of fatty acid–like ligands.
- PPARα acts in muscle, adipose tissue, and liver to turn on a set of genes essential for fatty acid oxidation, including the fatty acid transporter, carnitine acyltransferases I and II, fatty acyl–CoA dehydrogenases for short, medium, long, and very long acyl chains, and related enzymes.

- This response is triggered when a cell or organism has an increased demand for energy from fat catabolism (such as; during a fast between meals, under conditions of longer-term starvation).
- Glucagon, released in response to low blood glucose, can act through cAMP and the transcription factor CREB to turn on certain genes for lipid catabolism.

- Another situation that is accompanied by major changes in the expression of the enzymes of fatty acid oxidation is the transition from fetal to neonatal metabolism in the heart.
- In the fetus the principal fuels are glucose and lactate, but in the neonatal heart, fatty acids are the main fuel.
- At the time of this transition, PPARα is activated and in turn activates the genes essential for fatty acid metabolism.

- The major site of fatty acid oxidation, at rest and during exercise, is skeletal muscle.
- Endurance training increases PPARα expression in muscle, leading to increased levels of fatty acid–oxidizing enzymes and increased oxidative capacity of the muscle.