Lipid Metabolism

Classification of Lipids

Category	Sub-types	Characteristics
Simple Lipids (单纯脂类)	• **Acylglycerols (酰基甘油酯)** • **Waxes(蜡)**	Esters of fatty acids with various alcohols.
Complex Lipids (复合脂类)	• **Phospholipids(磷脂)** • **Glycolipids / Sulfolipids(糖/硫脂)**	Esters of fatty acids containing additional groups (e.g., phosphate, carbohydrates).
Non-saponifiable Lipids (非皂化脂类)	• **Terpenes(萜类)** • **Prostaglandins(前列腺素类)** • **Sterols (甾醇类)**	**Do not contain fatty acids** or ester bonds; cannot be hydrolyzed into soap.

Contents

Fat Catabolism (脂肪的分解代谢)

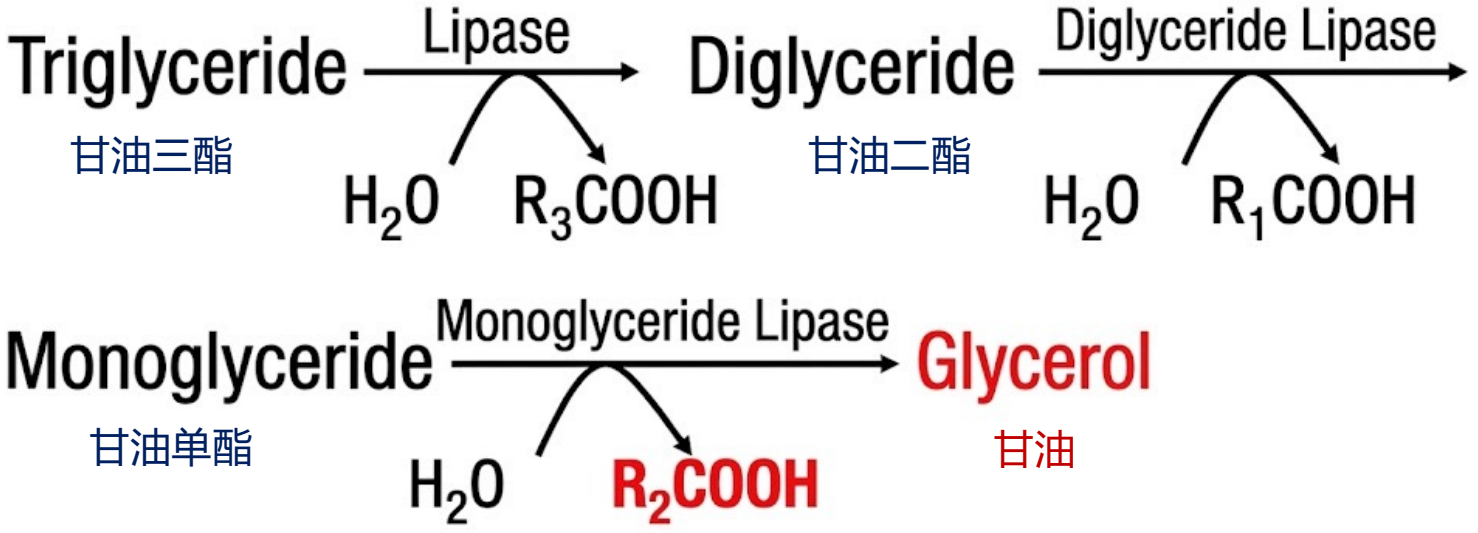
I. Enzymatic Hydrolysis of Triacylglycerols (脂肪的酶促降解)

Enzymatic hydrolysis of triacylglycerols (TAGs) is the biological process of breaking down fats into their constituent parts, glycerol and fatty acids, using water and specific enzymes called lipases (脂肪酶).

Fat Catabolism (脂肪的分解代谢)

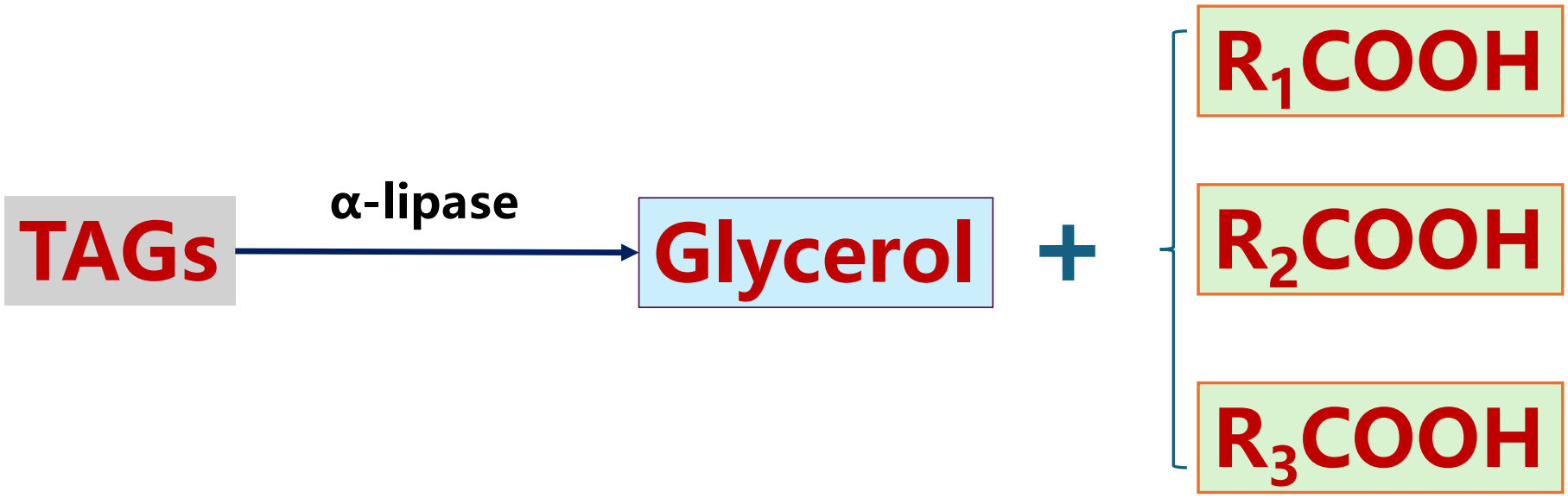
Animal Pathway: The Stepwise Breakdown

In animal tissues (especially in our adipose/fat cells), this is a sequential process. Each step releases one fatty acid chain.

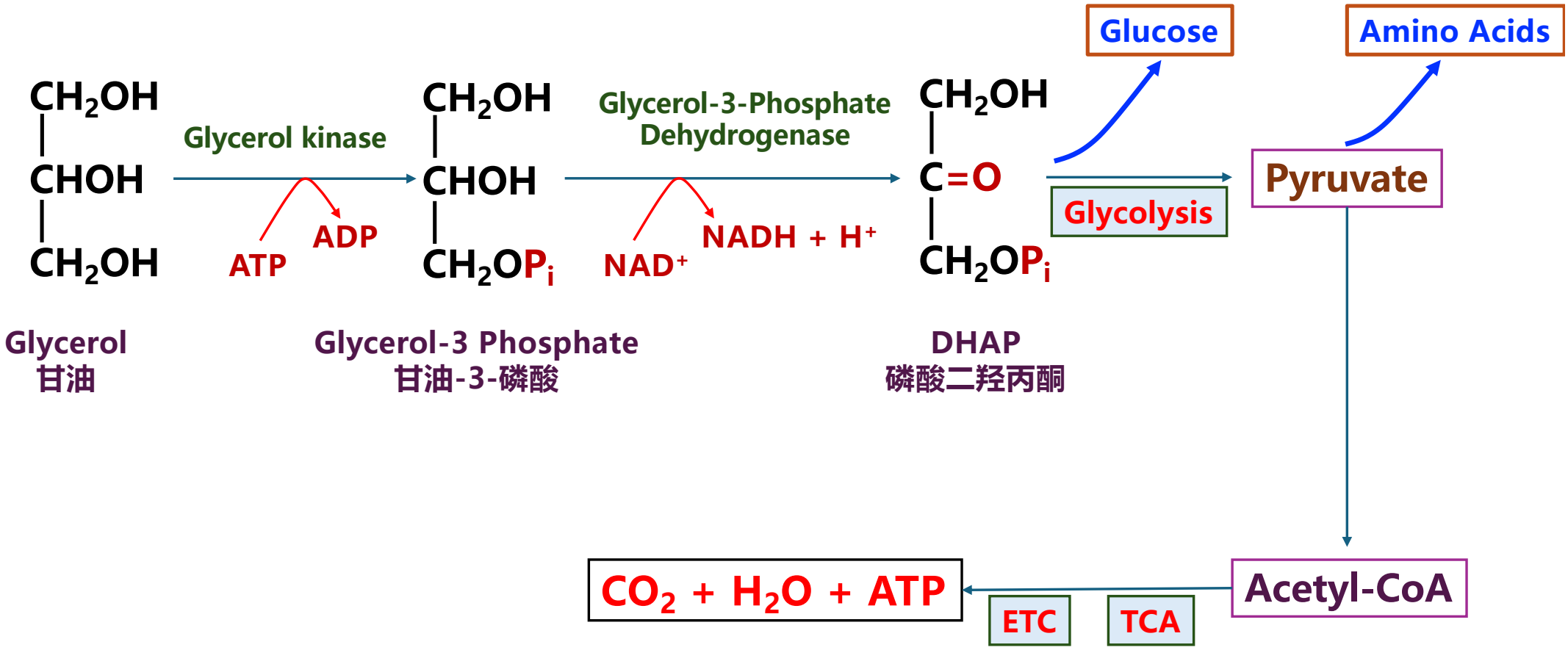


Fat Catabolism (脂肪的分解代谢)

In Plants



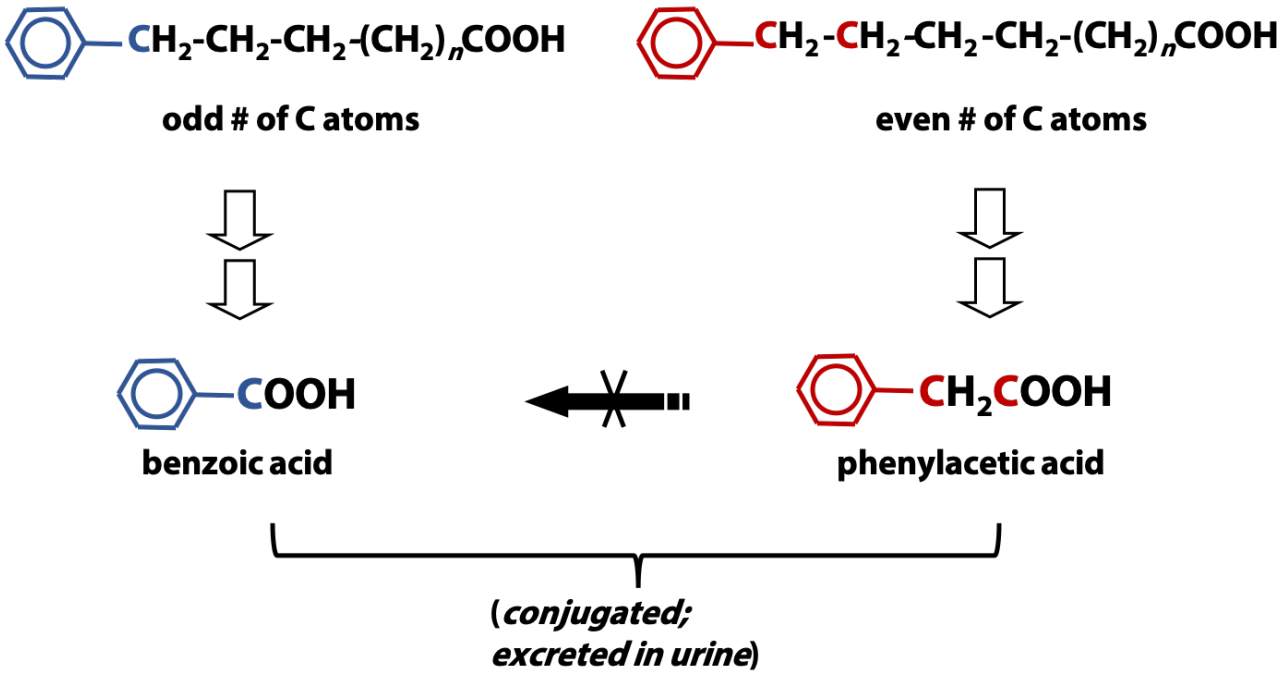
Fat Catabolism (脂肪的分解代谢)



Fat Catabolism (脂肪的分解代谢)

Elucidation of β oxidation (Franz Knoop; 1904)

Franz Knoop

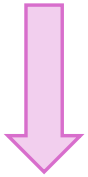


Fat Catabolism (脂肪的分解代谢)

β oxidation

The beta oxidation (also β-oxidation) is the catabolic process by which fatty acid molecules are broken down in the cytosol in prokaryotes and in the **mitochondria** in eukaryotes to generate acetyl-CoA.

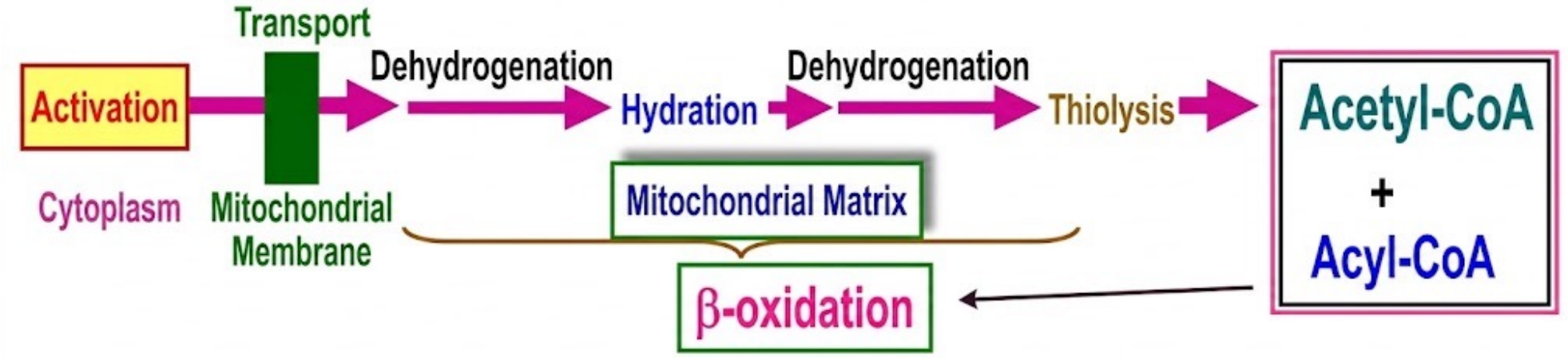
C_n-acyl-CoA + FAD + NAD^+ + H_2O + CoA



C_{n-2}-acyl-CoA + $FADH_2$ + NADH + H^+ + acetyl-CoA

Fat Catabolism (脂肪的分解代谢)

Overall



Fat Catabolism (脂肪的分解代谢)

The transport of fatty acids into the mitochondria

Why transport is needed

- **β-Oxidation occurs in the mitochondrial matrix.**
- **Long-chain fatty acyl-CoA cannot cross the inner mitochondrial membrane directly.**
- Therefore, the cell uses the **carnitine shuttle (肉碱穿梭)** to move the acyl group into the matrix.

Step 1: Activation

Fatty acids are activated to **fatty acyl-CoA** on the cytosolic side of the outer mitochondrial membrane.

Fatty acid + CoA

↓ ATP

↓ ADP

Fatty acyl-CoA

Step 2: Formation of acyl-carnitine

The fatty-acyl group transfers from CoA to carnitine by carnitine palmitoyltransferase I (CPT I), located on the outer mitochondrial membrane.

Fatty acyl-CoA + carnitine

肉毒碱转酰基酶I ↓

Fatty acyl-carnitine + CoA

Step 3: Across inner membrane

Carnitine-acylcarnitine translocase (**移位酶**) transports fatty acyl-carnitine into the mitochondrial matrix. At the same time, free carnitine is transported out.

Step 4: Reform fatty acyl-CoA

On the matrix side, carnitine palmitoyltransferase II (CPT II) transfers fatty acyl group back to CoA.

Fatty acyl-carnitine + CoA

↓肉毒碱转酰基酶II

Fatty acyl-CoA + carnitine

Fat Catabolism (脂肪的分解代谢)

The transport of fatty acids into the mitochondria

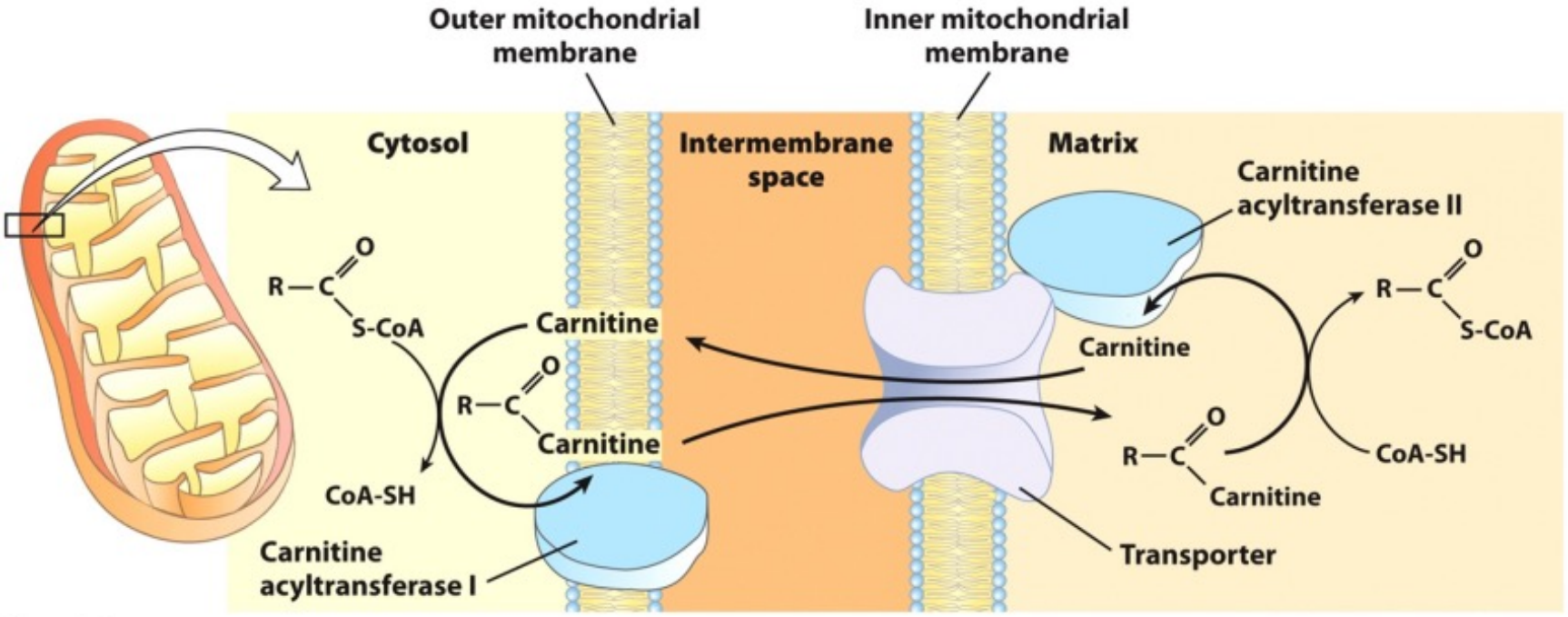


Figure 17-6
Lehninger Principles of Biochemistry, Sixth Edition

Fat Catabolism (脂肪的分解代谢)

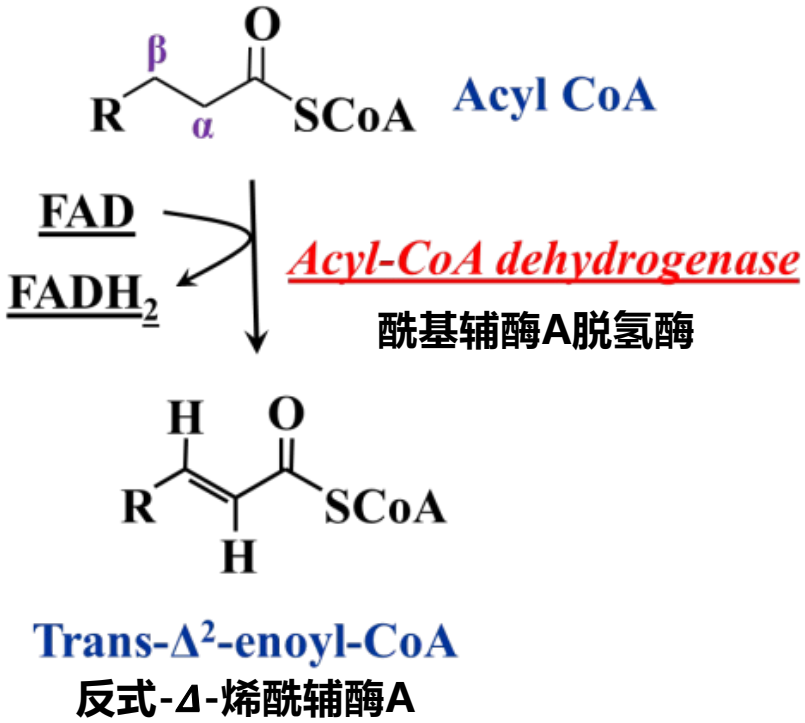
The beta oxidation pathway

Beta oxidation consists of four steps: Oxidation(脱氢), Hydration(水化), Oxidation (脱氢) and Thiolysis (硫解). Each pass-through beta oxidation removes one acetyl moiety in the form of acetyl CoA.

Step 1（脱氢）: Dehydrogenation by

FAD forms a double bond between the

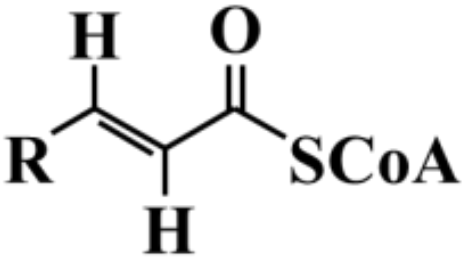
α and the β carbons of fatty acyl CoA



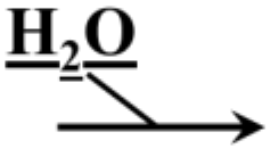
Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

Step 2（水化）: Water is added across the double bond to give an alcohol at the beta carbon

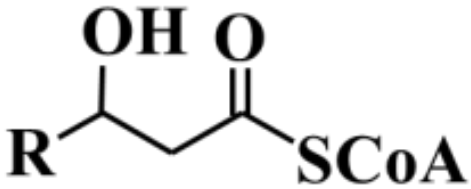


Trans-Δ^2-enoyl-CoA



Enoyl-CoA hydratase

烯酰辅酶A水化酶



L-β-hydroxy-acyl-CoA

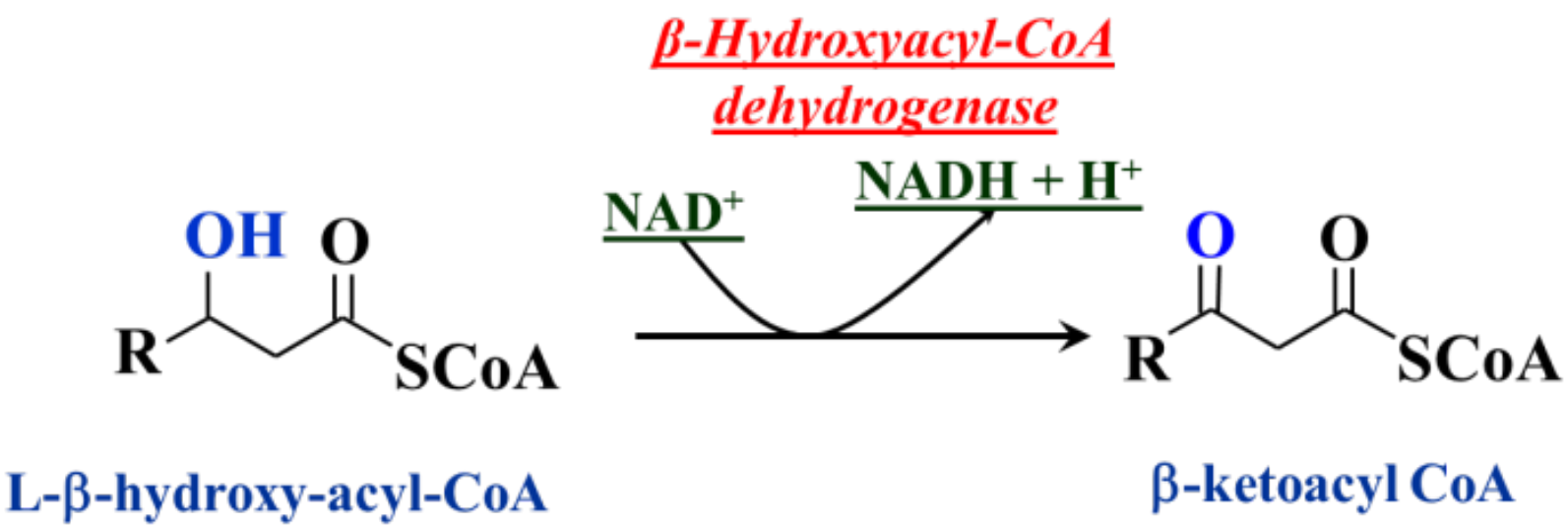
L-β-羟酰辅酶A

Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

Step 3（再脱氢）: Oxidation of the alcohol by NAD+

β-羟酰辅酶A脱氢酶

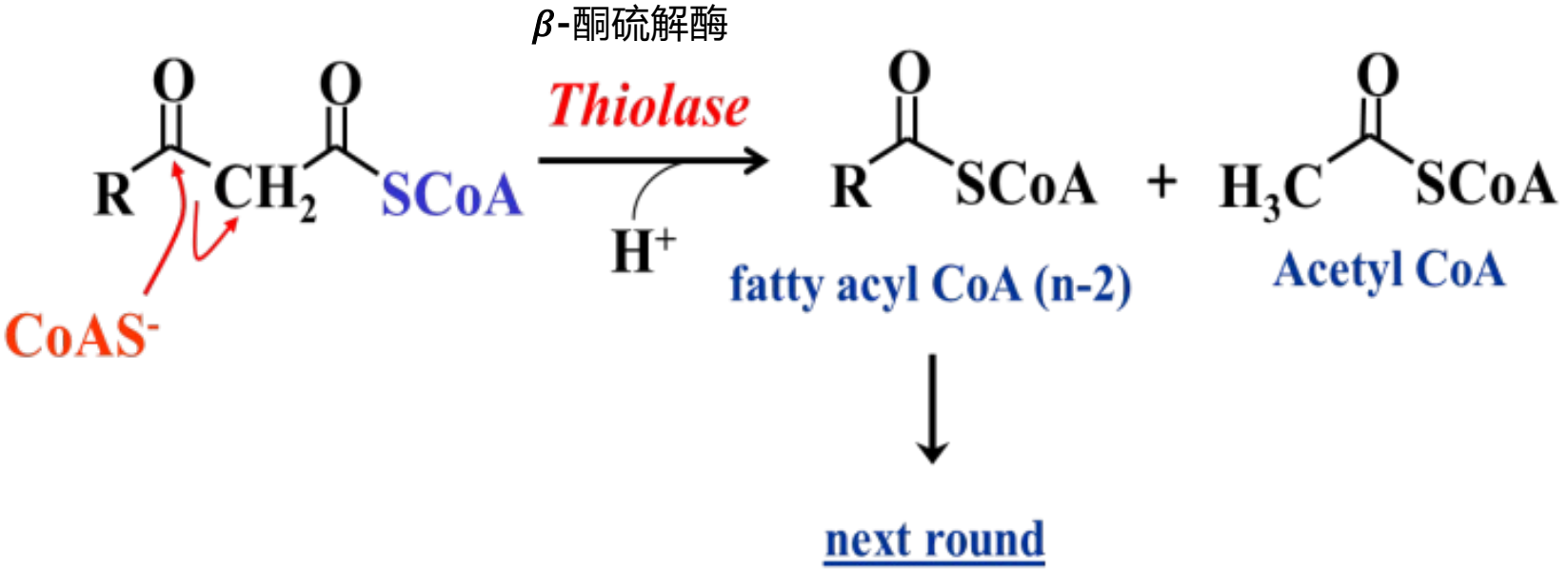


β-酮酰辅酶A

Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

Step 4 （硫解）: β-keto acyl CoA reacts with coenzyme A, releasing its carboxyl-terminal two carbon fragment as acetyl CoA

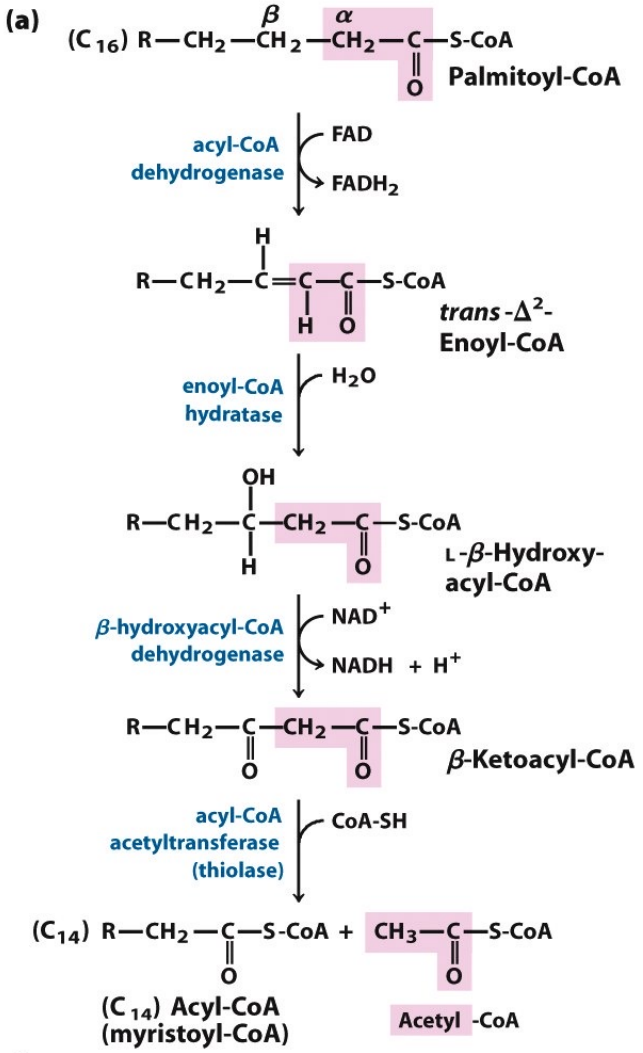


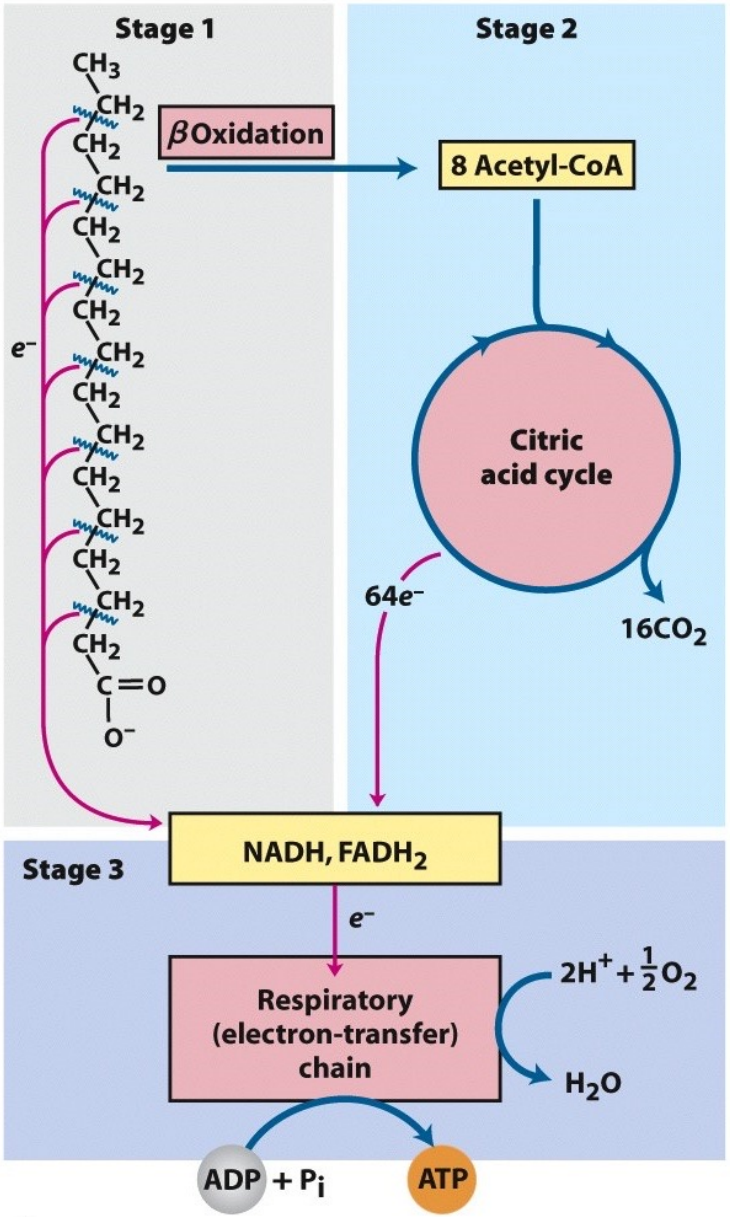
Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

How many rounds of beta oxidation are required to convert palmitoyl CoA (C16:0) into eight Acetyl CoA molecules?

- 1 $FADH_2$ is formed in each turn (7 $FADH_2$ in total)
- 1 NADH is formed in each turn (7 NADH in total)





(1) Entry into TCA

以软脂酸（C_{16}）为例：

$CH_3(CH_2)_{14}COOH$ $\xrightarrow[ATP \quad AMP + PPi]{CoASH}$ $CH_3(CH_2)_{14}C\sim CoA$

7 CoASH　　7次β-氧化

$8CH_3C\sim CoA$　　$7FADH_2$　　$7NADH$

Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

(2) Entry into the Glyoxylate Cycle

Glyoxylate cycle(乙醛酸循环): A modified form of the citric acid cycle in which acetyl-CoA produced from fatty acid β-oxidation is converted into succinate (琥珀酸) through a series of enzymatic reactions in the glyoxysome (乙醛酸体). 乙醛酸循环与TCA循环共享大部分反应，但它“绕过”了TCA循环中释放 CO_2的步骤。

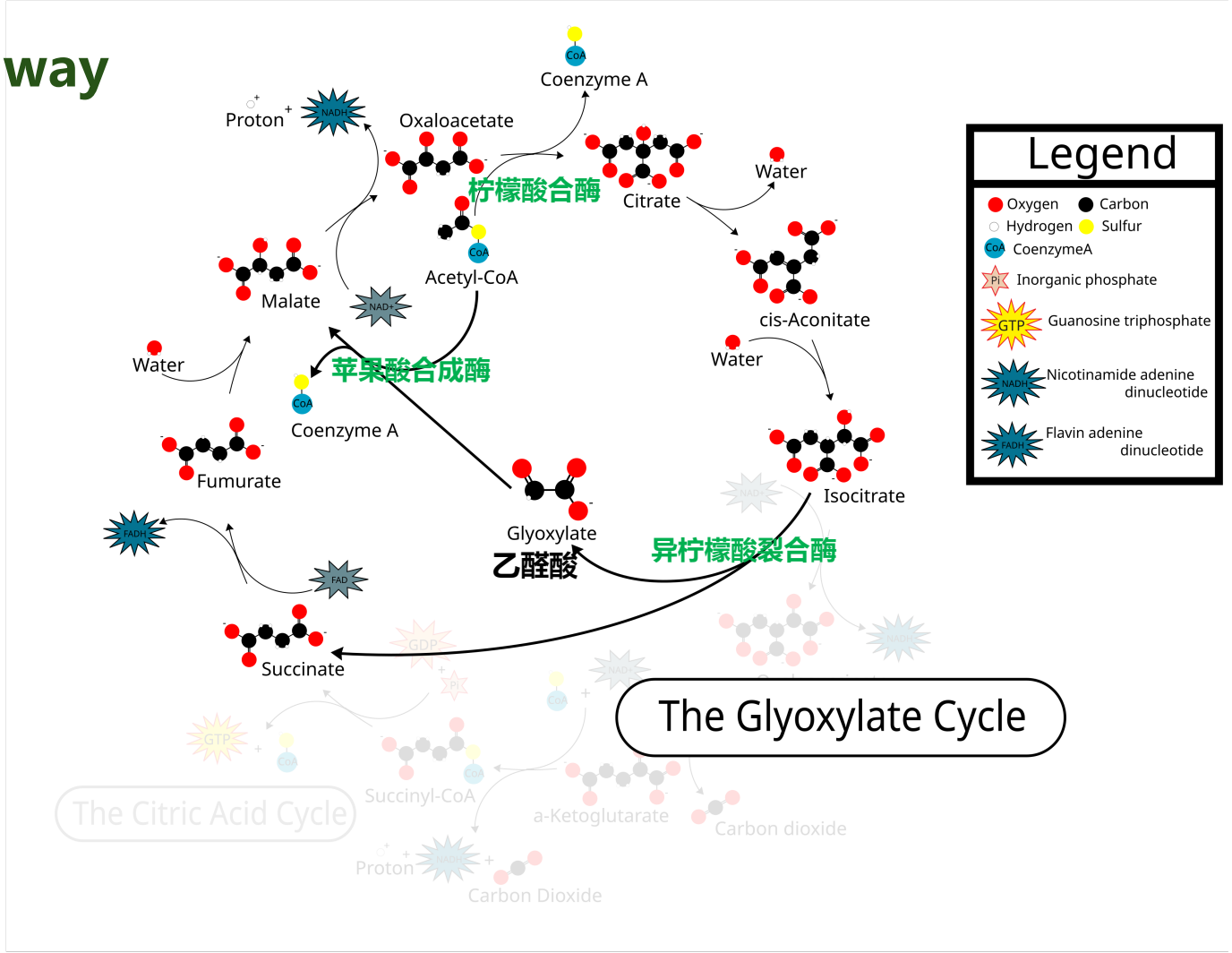
Two key enzymes distinguish the glyoxylate cycle:

- **Isocitrate lyase 异柠檬酸裂合酶**
- **Malate synthase 苹果酸合成酶**

Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

(2) Entry into the Glyoxylate Cycle



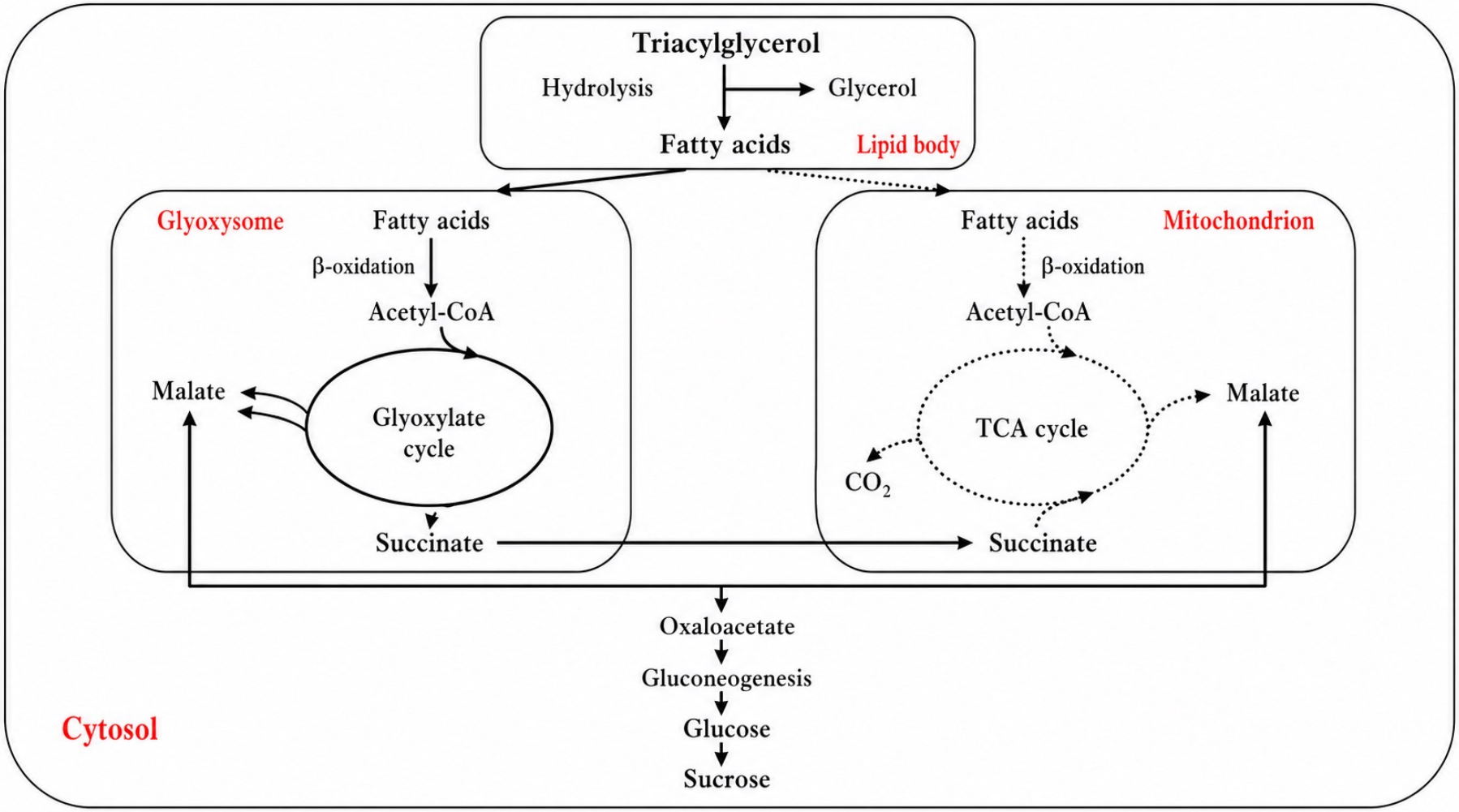
Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

(2) Entry into the Glyoxylate Cycle

Biological Significance of the Glyoxylate Cycle

- Enables plants and many microorganisms to convert **fatty acid carbon into carbohydrates**.
- Especially important during **seed germination**, when stored lipids provide carbon and energy.
- Functions as a modified branch of the **citric acid cycle**.
- Produces **succinate**, which can replenish four-carbon intermediates and support **gluconeogenesis(糖异生)**.


Triacylglycerol
Hydrolysis
Glycerol
Fatty acids
Lipid body
Glyoxysome
Fatty acids
β-oxidation
Acetyl-CoA
Malate
Glyoxylate cycle
Succinate
Fatty acids
Mitochondrion
β-oxidation
Acetyl-CoA
TCA cycle
Malate
CO_2
Succinate
Oxaloacetate
Gluconeogenesis
Glucose
Sucrose
Cytosol

Fat Catabolism (脂肪的分解代谢)

The beta oxidation pathway

(3) In Animal Liver Cells, Acetyl-CoA Converts into Ketone Bodies (酮体)

When fatty acid β-oxidation produces more acetyl-CoA than can be processed by the citric acid cycle, liver mitochondria convert acetyl-CoA into ketone bodies.

Fatty acids → β-oxidation → acetyl-CoA

in liver mitochondria → ketone bodies → blood → extrahepatic tissues

Fat Catabolism (脂肪的分解代谢)

The α-Oxidation pathway

α-Oxidation removes one carbon from the carboxyl end of a fatty acid. **It is especially important for branched-chain fatty acids that cannot undergo normal β-oxidation.**

Key examples:

- In plants, α-oxidation can generate **odd-chain fatty acids**.
- In animals, α-oxidation is essential for the breakdown of **branched-chain fatty acids,** especially **phytanic acid (植烷酸).**
- Defects in phytanic acid α-oxidation cause **Refsum disease**.

Refsum disease（雷夫叙姆病）

Differences Between α-Oxidation and β-Oxidation

β-Oxidation

- Occurs mainly in **mitochondria**.
- Acts on the **β-carbon** of fatty acyl-CoA.
- Removes two-carbon units as **acetyl-CoA**.
- Produces **acetyl-CoA, NADH, and $FADH_2$**.
- Main pathway for complete fatty acid oxidation and ATP production.

α-Oxidation

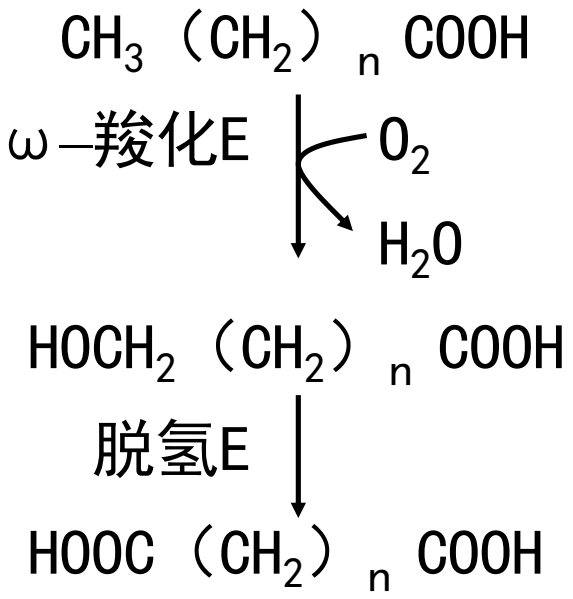
- Occurs mainly in **peroxisomes**.
- Acts on the **α-carbon** of fatty acids.
- Important for degradation of **branched-chain fatty acids**, especially **phytanic acid**.
- Removes **one carbon**.
- Produces a fatty acid shortened by one carbon, which can then enter β-oxidation.

Fat Catabolism (脂肪的分解代谢)

The ω-Oxidation pathway

ω-Oxidation is the oxidation of the terminal methyl carbon, the ω-carbon, of a fatty acid. Its products are α,ω-dicarboxylic acids, which contain carboxyl groups at both ends.

- Oxidizes the terminal methyl (甲基) group, also called the **ω-carbon**.
- Converts fatty acids into **α,ω-dicarboxylic acids**.
- Serves as an auxiliary pathway (辅助途径) when **β-oxidation is impaired**.
- Dicarboxylic acids (二羧酸) can undergo further **β-oxidation**.



Contents

De Novo Fatty Acid Synthesis 脂肪酸生物合成

- Occurs in the **cytosol**.
- Produces saturated fatty acids up to **C16**, mainly **palmitate(棕榈酸)**.
- Uses **acetyl-CoA** as the initial carbon source.
- Uses **malonyl-CoA (丙二酸单酰CoA)** as the direct donor for chain elongation.
- Requires **NADPH** as the reducing power.
- A major source of NADPH is the **pentose phosphate pathway**.

De Novo Fatty Acid Synthesis 脂肪酸生物合成

Sources of acetyl-CoA

Acetyl-CoA can be produced from:

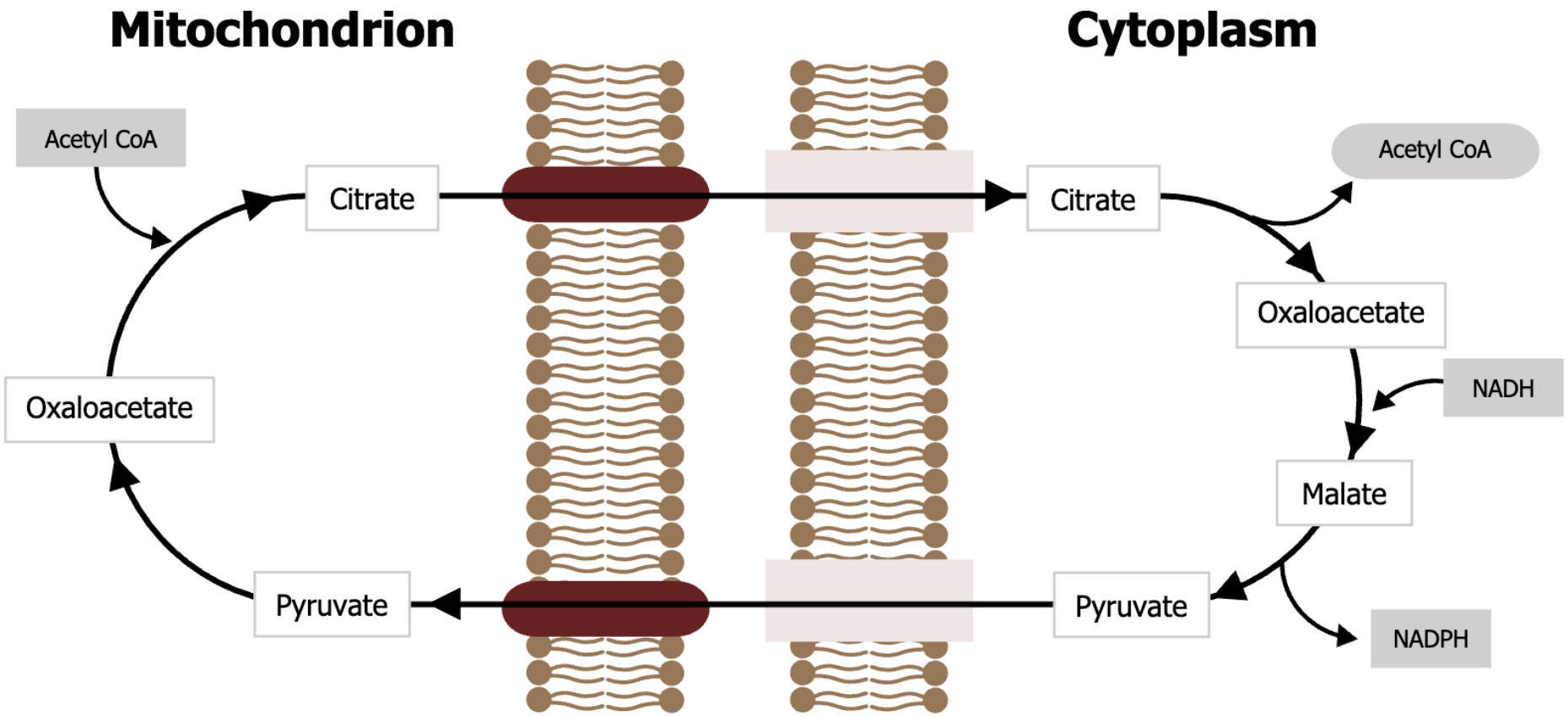
- **Oxidative decarboxylation of pyruvate**
- **β-oxidation of fatty acids**
- **Oxidative degradation of amino acids**

Cellular location and transport

- Acetyl-CoA is mainly generated in the **mitochondria**. However, fatty acid synthesis occurs in the **cytosol**.
- Acetyl-CoA cannot directly cross the inner mitochondrial membrane, and its carbon is exported as **citrate** through the **citrate shuttle**.

柠檬酸穿梭

De Novo Fatty Acid Synthesis 脂肪酸生物合成



Citrate shuttle

Review: Mitochondrial Transport Systems

1. Cytosolic NADH → Mitochondria

- Glycerol phosphate shuttle / 磷酸甘油穿梭
- Malate-aspartate shuttle / 苹果酸穿梭

2. Cytosolic fatty acyl-CoA → Mitochondria

- Carnitine shuttle / 肉毒碱穿梭

3. Mitochondrial acetyl-CoA → Cytosol

- Citrate shuttle / 柠檬酸穿梭

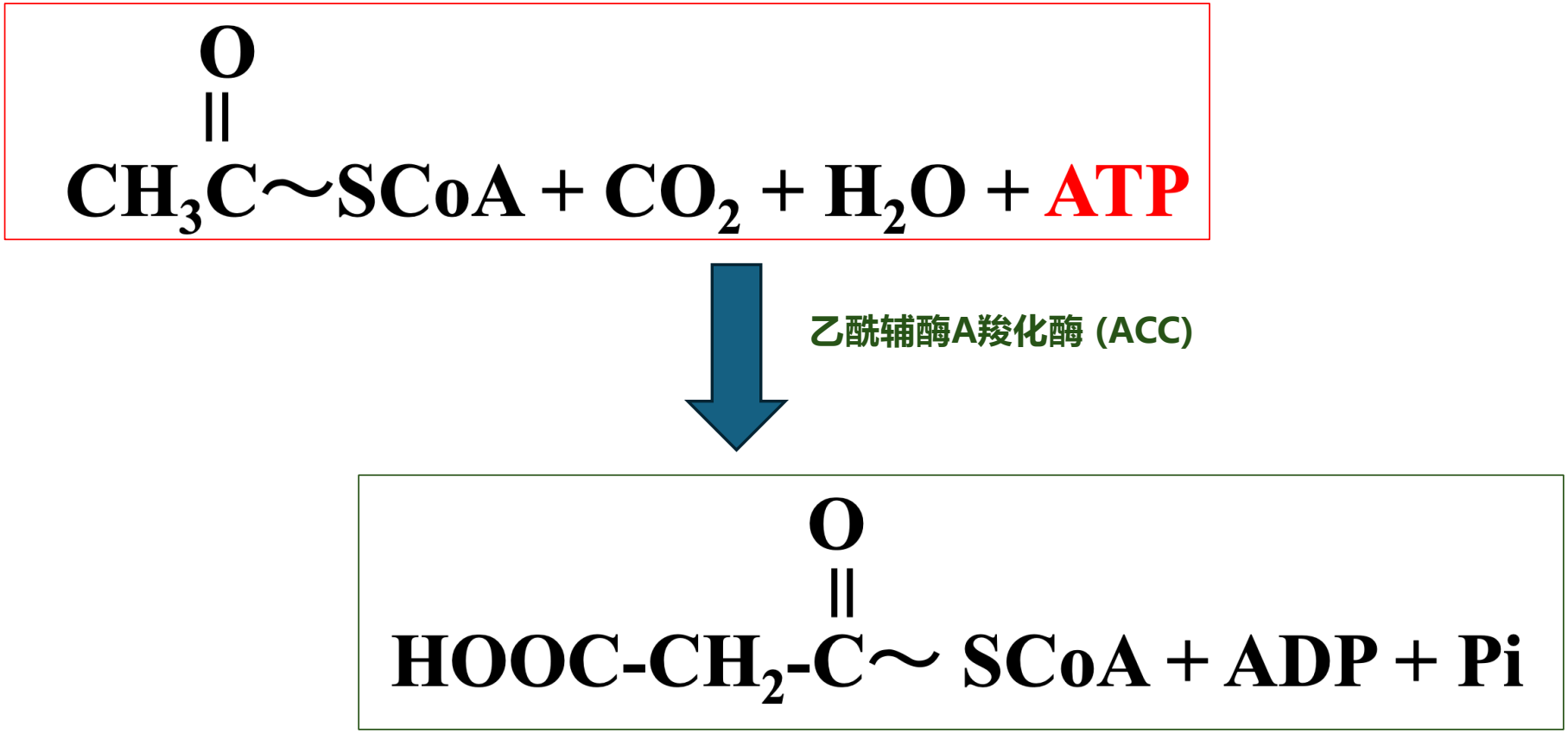
De Novo Fatty Acid Synthesis 脂肪酸生物合成

Formation of Malonyl-CoA/丙二酸单酰CoA

- Malonyl-CoA is produced by carboxylation of acetyl-CoA.
- The reaction is catalyzed by acetyl-CoA carboxylase (ACC；乙酰CoA羧化酶).
- Biotin(生物素) is the prosthetic group(辅基) that carries CO_2.
- Malonyl-CoA is the immediate two-carbon donor for fatty acid chain elongation.

De Novo Fatty Acid Synthesis 脂肪酸生物合成

Formation of Malonyl-CoA/丙二酸单酰CoA

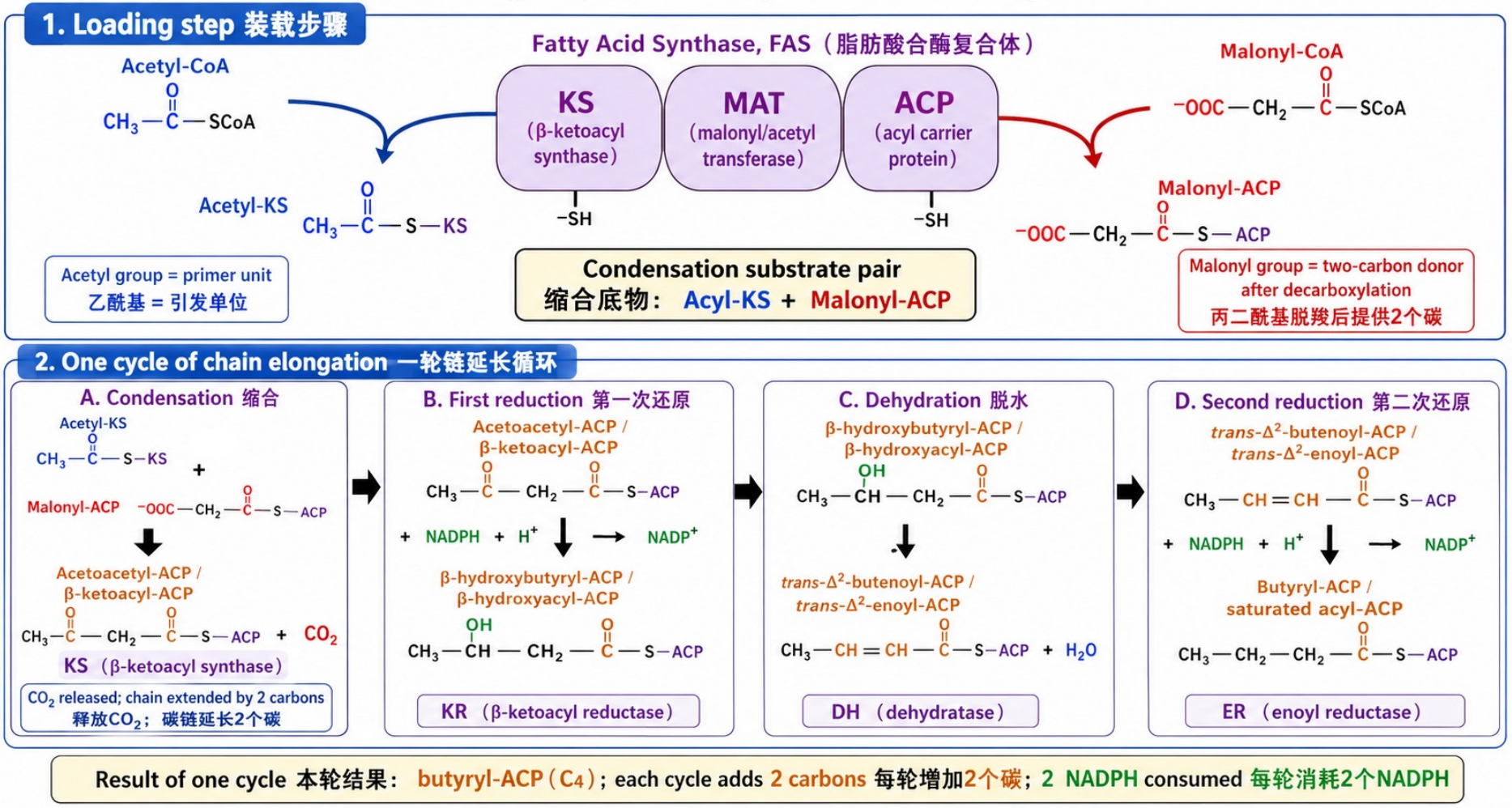


De Novo Fatty Acid Synthesis 脂肪酸生物合成

Fatty Acid Synthase: Enzyme System

- **One carrier protein: ACP — acyl carrier protein/酰基载体蛋白**
- **Six catalytic activities:**
  - ✓ AT: acetyl transferase 乙酰基转移酶
  - ✓ MT: malonyl transferase 丙二酰基转移酶
  - ✓ KS : β-ketoacyl-ACP synthase β-酮脂酰-ACP合酶
  - ✓ KR : β-ketoacyl-ACP reductase β-酮脂酰-ACP还原酶
  - ✓ DH: β-hydroxyacyl-ACP dehydratase β-羟脂酰-ACP脱水酶
  - ✓ ER: enoyl-ACP reductase 烯酰-ACP还原酶

De Novo Fatty Acid Synthesis 脂肪酸生物合成



De Novo Fatty Acid Synthesis 脂肪酸生物合成

Overall Reaction of Palmitate Synthesis

- **The synthesis of palmitate from acetyl-CoA can be divided into two stages:**

1. **Formation of 7 malonyl-CoA molecules**
2. **Seven cycles of fatty acid chain elongation**

Acetyl-CoA + 7 Malonyl-CoA + 14 NADPH + 14 H^+

Palmitate + 7 CO_2 + 8 CoA-SH + 14 $NADP^+$ + 6 H_2O

Fatty Acid Synthesis vs. β-Oxidation

	Fatty Acid Synthesis	β-Oxidation
Location	Cytosol	Mitochondria
Carrier	ACP	CoA
2C unit	Malonyl-CoA / Malonyl-ACP 丙二酰-CoA / 丙二酰-ACP	Acetyl-CoA 乙酰-CoA
Redox cofactors 氧化还原辅酶	NADPH as electron donor	NAD^+ and FAD as electron acceptors
Enzyme system 酶系统	Fatty acid synthase: 6 enzymes + ACP	Four separate enzymes
Energy	Consumes 7 ATP and 14 NADPH	Produces 7 NADH and 7 $FADH_2$
Transport system 转运系统	Citrate shuttle 柠檬酸穿梭	Carnitine shuttle 肉碱穿梭
Direction	Builds the chain toward the carboxyl end	Degrades from the carboxyl end

De Novo Fatty Acid Synthesis 脂肪酸生物合成

Elongation of Saturated Fatty Acids

- In animals, fatty acid elongation occurs mainly in the **endoplasmic reticulum** and, to a lesser extent, in **mitochondria**.
- The elongation process resembles the reverse of β-oxidation, but the two pathways are not identical.

De Novo Fatty Acid Synthesis 脂肪酸生物合成

Biosynthesis of Unsaturated Fatty Acids

- **In animals and fungi**, fatty acyl-CoA is desaturated by membrane-bound desaturases(去饱和酶). Electrons are supplied by NADH or NADPH and transferred through cytochrome b_5 or related electron carriers.
- **In plants**, desaturation occurs mainly on fatty acids esterified to ACP or membrane lipids. Reducing power: NADPH