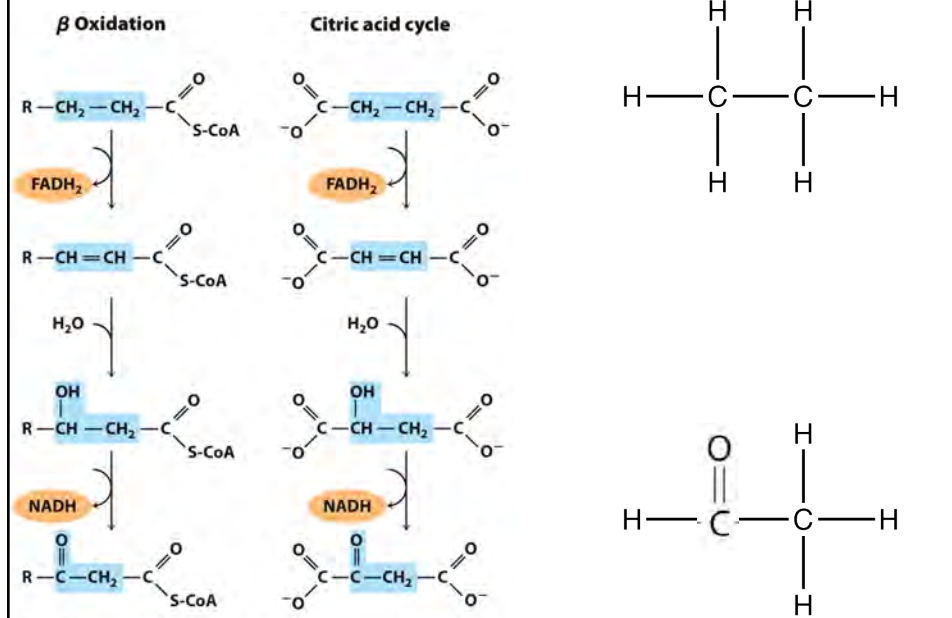
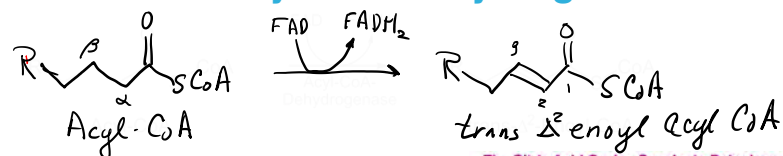


# Fatty Acid Degradation



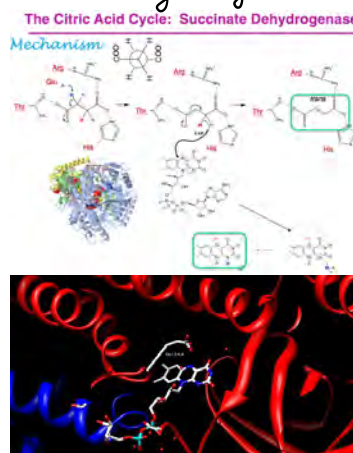
# Fatty Acid Degradation

## $\beta$ -Oxidation: Acyl-CoA Dehydrogenase



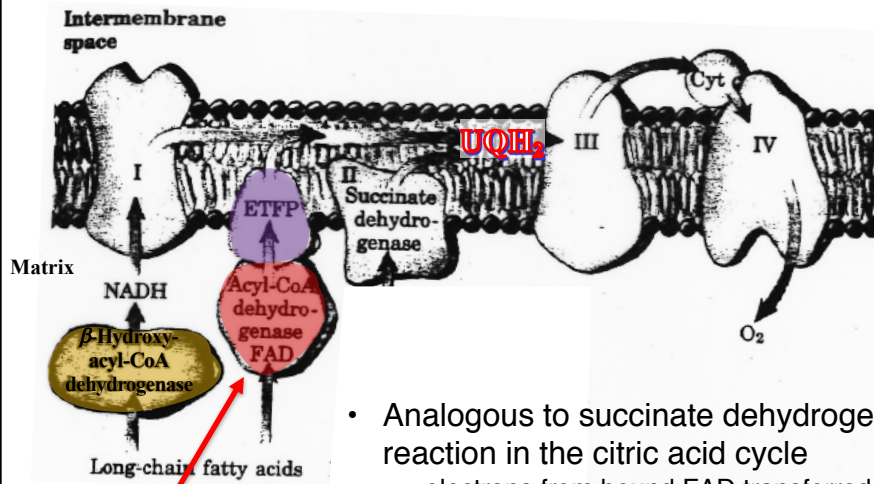
- Catalyzed by **isoforms** of **acyl-CoA dehydrogenase (AD)** on the **inner-mitochondrial membrane**
  - very-long-chain AD (12–18 carbons)\*
  - medium-chain AD (4–14 carbons)
  - short-chain AD (4–8 carbons)
- Results in **trans double bond**, different from naturally occurring unsaturated fatty acids
- Mechanism same as succinate dehydrogenase

\*Adrenoleukodystrophy (ALD)



## Fatty Acid Degradation

### $\beta$ -Oxidation: Acyl-CoA Dehydrogenase

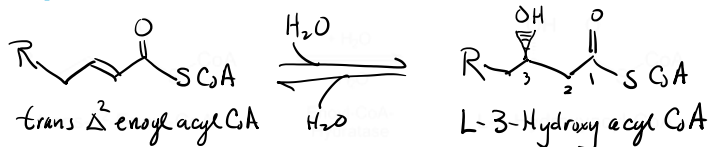


Different isozymes bind to same ETF

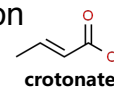
- Analogous to succinate dehydrogenase reaction in the citric acid cycle
  - electrons from bound FAD transferred directly to the electron- transport chain via **electron-transferring flavoprotein (ETF)**

## Fatty Acid Degradation

### $\beta$ -Oxidation: Enoyl-CoA hydratase



- Catalyzed by two isoforms of **enoyl-CoA hydratase**:
  - soluble short-chain hydratase (crotonase)
  - membrane-bound long-chain hydratase, part of **trifunctional protein (TFP)**
- **Water adds** across the double bond yielding alcohol on  $\beta$  carbon.
- Specific for single *trans*- $\Delta^2$  double bond, no conjugation
- Sometimes called crotonase
- Analogous to fumarase reaction in the citric acid cycle
  - same stereo-specificity



## Fatty Acid Degradation

### $\beta$ -Oxidation: $\beta$ -hydroxyacyl-CoA dehydrogenase



- Catalyzed by  $\beta$ -hydroxyacyl-CoA dehydrogenase
- The enzyme uses **NAD cofactor** as the hydride acceptor.
- **Only L-isomers** of hydroxyacyl CoA act as substrates.
- Analogous to malate dehydrogenase reaction in the citric acid cycle and the lactate dehydrogenase in fermentation

## Fatty Acid Degradation

### $\beta$ -Oxidation: Thiolase



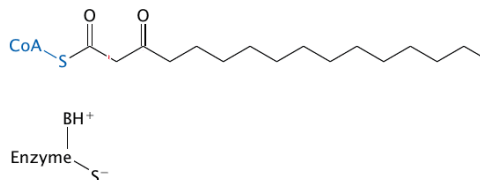
- Catalyzed by **acyl-CoA acetyltransferase** (thiolase) via covalent mechanism
  - The carbonyl carbon in  $\beta$ -ketoacyl-CoA is **electrophilic**.
  - Active-site thiolate acts as a nucleophile and releases acetyl-CoA.
  - Terminal sulfur in **CoA-SH** acts as a nucleophile and **picks up the fatty acid** chain from the enzyme.
- **The net reaction is thiolysis of the carbon-carbon bond.**

# Fatty Acid Degradation

## Mechanism

- The carbonyl carbon in  $\beta$ -ketoacyl-CoA is **electrophilic**.
- Active-site thiolate acts as a nucleophile and releases acetyl-CoA.
- Terminal sulfur in **CoA-SH** acts as a nucleophile and **picks up the fatty acid** chain from the enzyme.

## $\beta$ -Oxidation: Thiolase

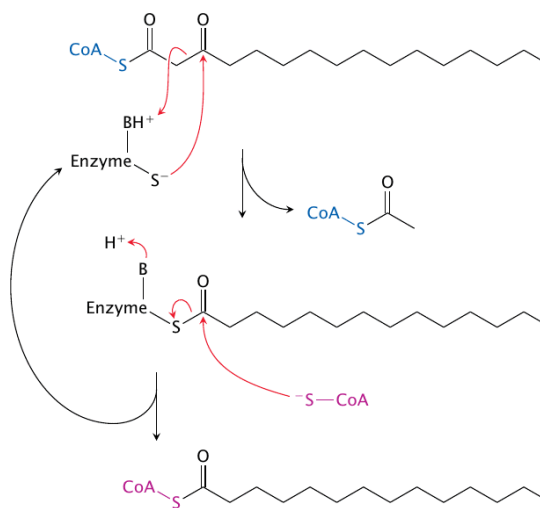


# Fatty Acid Degradation

## Mechanism

- The carbonyl carbon in  $\beta$ -ketoacyl-CoA is **electrophilic**.
- Active-site thiolate acts as a nucleophile and releases acetyl-CoA.
- Terminal sulfur in **CoA-SH** acts as a nucleophile and **picks up the fatty acid** chain from the enzyme.

## $\beta$ -Oxidation: Thiolase



## Fatty Acid Degradation

### The $\beta$ -Oxidation Pathway

palmitic acid ( $C_{16} \rightarrow C_{14}$ )

How much energy from palmitate?

- For palmitic acid ( $C_{16}$ )
  - Repeating the previous four-step process six more times (seven total) results in **eight molecules of acetyl-CoA**.
    - $FADH_2$  is formed in each cycle (seven total).
    - $NADH$  is formed in each cycle (seven total).
- The 8 Acetyl-CoA molecules enters citric acid cycle and further oxidizes into  $CO_2$ .
  - This makes more GTP,  $NADH$ , and  $FADH_2$  (8, 24, 8, respectively)
- Electrons from all  $FADH_2$  (15) and  $NADH$  (31) enter the respiratory chain.

## Fatty Acid Degradation

### Energy from Fatty Acid Catabolism

**TABLE 17-1** Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to  $CO_2$  and  $H_2O$

Enzyme catalyzing the oxidation step	Number of $NADH$ or $FADH_2$ formed	Number of ATP ultimately formed <sup>a</sup>
<b><math>\beta</math> Oxidation</b>		
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
$\beta$ -Hydroxyacyl-CoA dehydrogenase	7 $NADH$	17.5
<b>Citric acid cycle</b>		
Isocitrate dehydrogenase	8 $NADH$	20
$\alpha$ -Ketoglutarate dehydrogenase	8 $NADH$	20
Succinyl-CoA synthetase	15	8 <sup>b</sup>
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 $NADH$	20
Total		108 – 2 = 106*

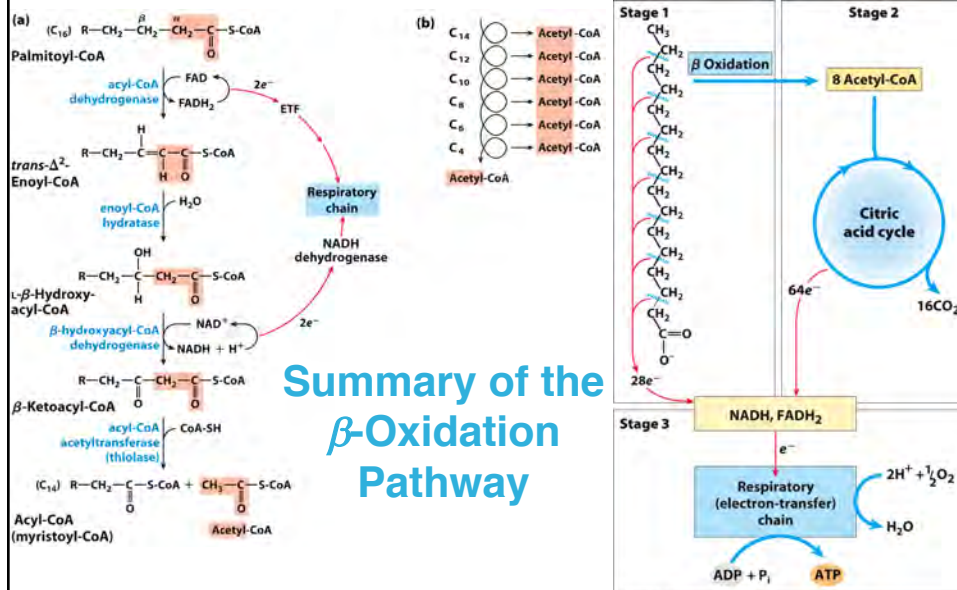
<sup>a</sup>These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per  $FADH_2$  oxidized and 2.5 ATP per  $NADH$  oxidized.

<sup>b</sup>GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 516).

\*These 2 "ATP" equivalents were expended in the activation by **Fatty acyl-CoA synthetase**.

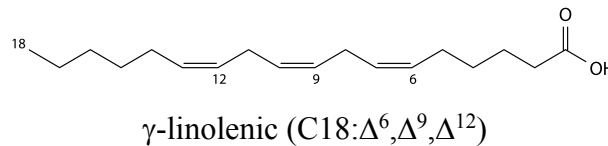
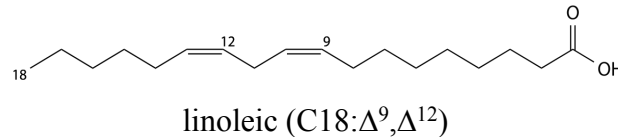
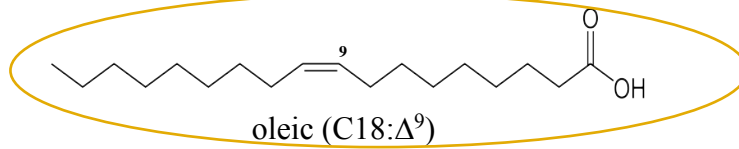
# Fatty Acid Degradation

Each pass removes one **acetyl moiety** in the form of acetyl-CoA.

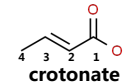


## Degradation of Unsaturated Fatty Acids

# Degradation of Unsaturated Fatty Acids



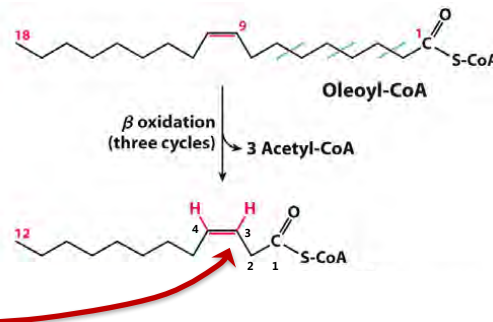
TWO problems:  
1. *cis*  
2. odd



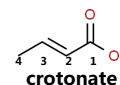
## Fatty Acid Degradation

- Naturally occurring unsaturated fatty acids contain *cis* double bonds.

- are NOT a substrate for enoyl-CoA hydratase
- Bond is *cis* and Δ<sup>3</sup>

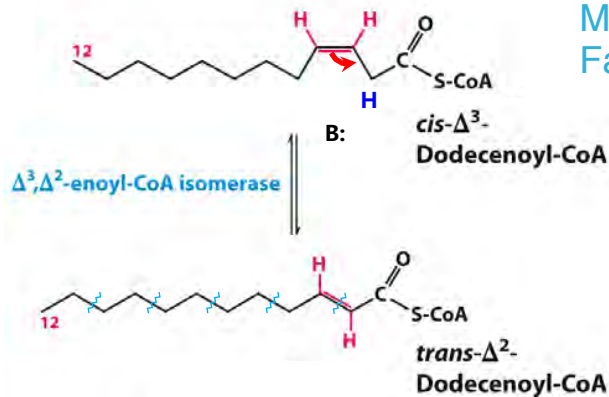


- Two additional enzymes are required.
  - isomerase**: converts *cis* double bonds starting at carbon 3 to trans double bonds at carbon 2
  - reductase**: reduces *cis* double bonds not at carbon 3
- Monounsaturated fatty acids require the **isomerase**.
- Polyunsaturated fatty acids require both enzymes.



## Fatty Acid Degradation

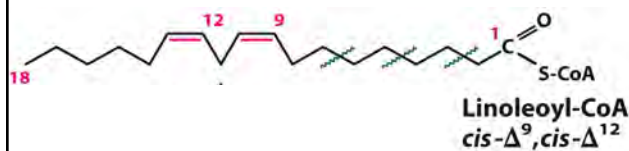
### Monounsaturated Fatty Acids



During first of five remaining cycles, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer  $\text{FADH}_2$ .

## Fatty Acid Degradation

### Oxidation of Polyunsaturated Fatty Acids Isomerization

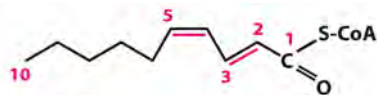


During first cycle, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer  $\text{FADH}_2$ .

This conjugated situation is not a substrate for the hydratase



## Fatty Acid Degradation



Oxidation of  
Polyunsaturated  
Fatty Acids  
Reductase

During first of four  
remaining cycles, acyl-  
CoA dehydrogenase  
step is skipped,  
resulting in 1 fewer  
 $\text{FADH}_2$ .

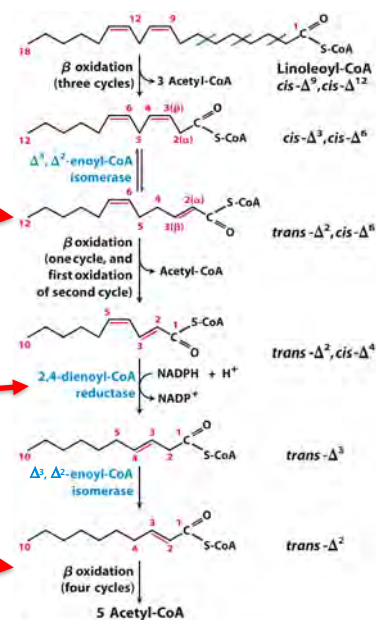
## Fatty Acid Degradation

Oxidation of  
Polyunsaturated Fatty  
Acids

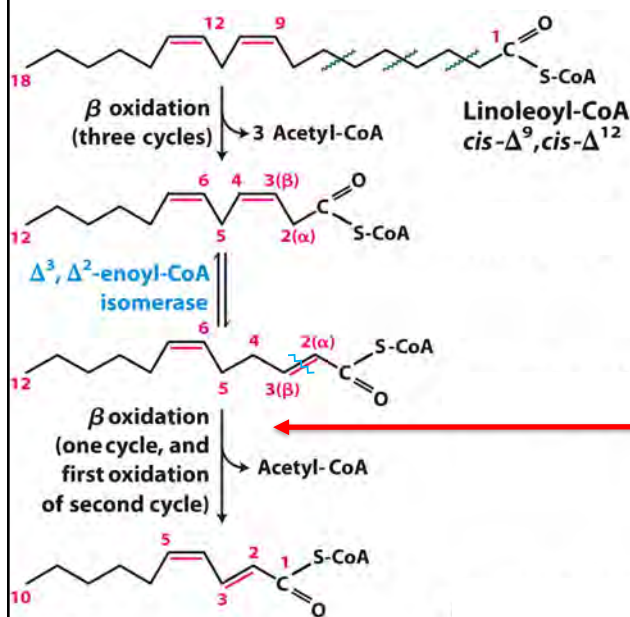
Results in 1 fewer  $\text{FADH}_2$  after  
isomerization (skips acyl-CoA  
dehydrogenase). Goes right to  
hydratase.

NADPH reduces the  
remaining unsaturated  
bond, resulting in no  
further loss of  $\text{FADH}_2$ .

Results in 1 fewer  $\text{FADH}_2$   
after isomerization.



## Fatty Acid Degradation

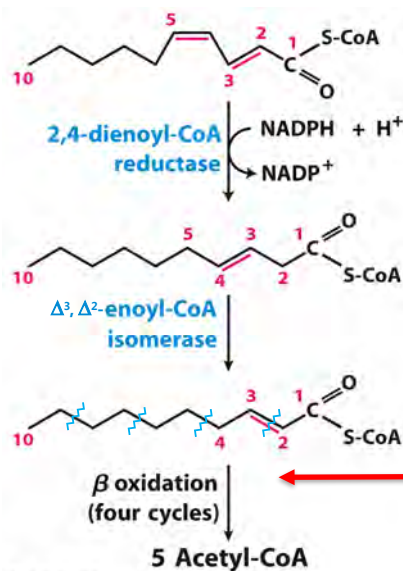


**Oxidation of Polyunsaturated Fatty Acids**  
Isomerization

During first cycle, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer  $\text{FADH}_2$ .

This conjugated situation is not a substrate for the hydratase

## Fatty Acid Degradation



**Oxidation of Polyunsaturated Fatty Acids**  
Reductase

During first of four remaining cycles, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer  $\text{FADH}_2$ .

# Degradation of Odd-Chain Fatty Acids

## Fatty Acid Degradation

### Oxidation of Odd-Numbered Fatty Acids

- Most dietary fatty acids are even-numbered.
- Many plants and some marine organisms also synthesize **odd-numbered fatty acids**.
- The metabolism of oxidation of odd-chain fatty acids CONVERGES with that of some amino acids
- Details will be discussed with amino acids

