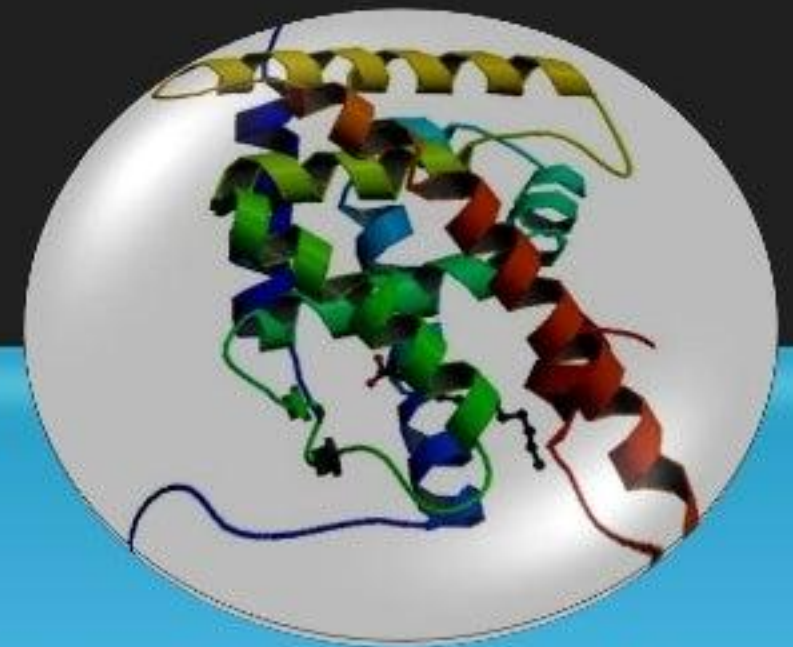
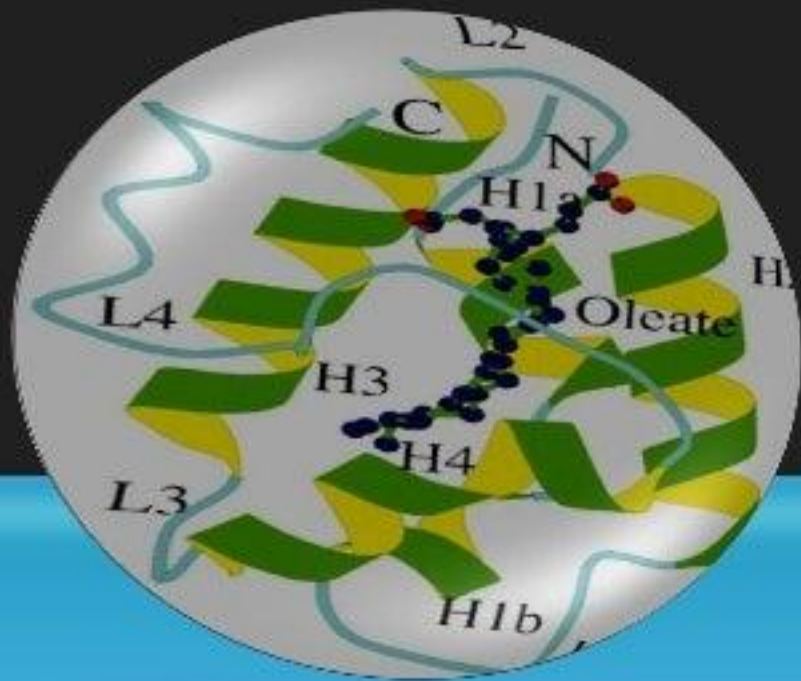


# BIOSYNTHESIS OF FATTY ACIDS



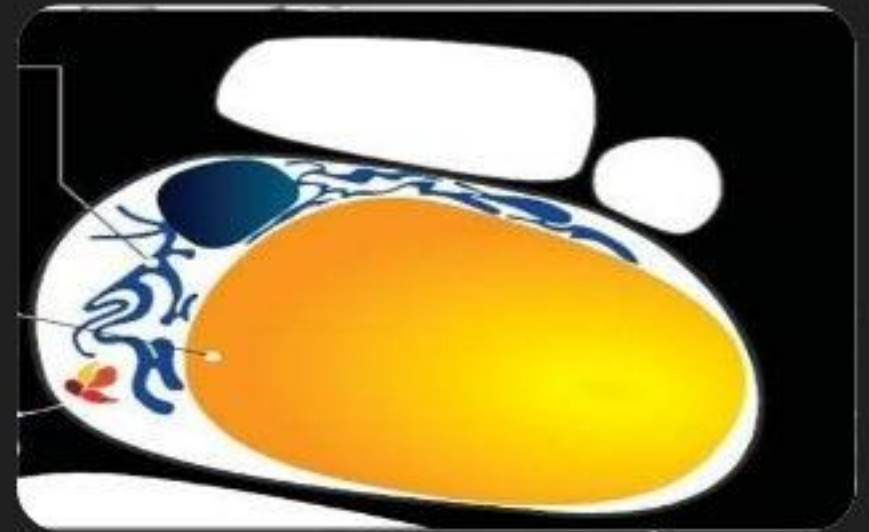
Presented by:- Anamika Banerjee



# Introduction

Fatty acids have 4 major physiological roles:

- 🔑 fatty acids are building blocks of phospholipids and glycolipids
- 🔑 many proteins are modified by the covalent attachment of fatty acids, which targets them to membrane locations.
- 🔑 fatty acids are fuel molecules
- 🔑 fatty acid derivatives serve as hormones and intracellular messengers.



# Fatty Acid Synthesis v/s Degradation

## SYNTHESIS

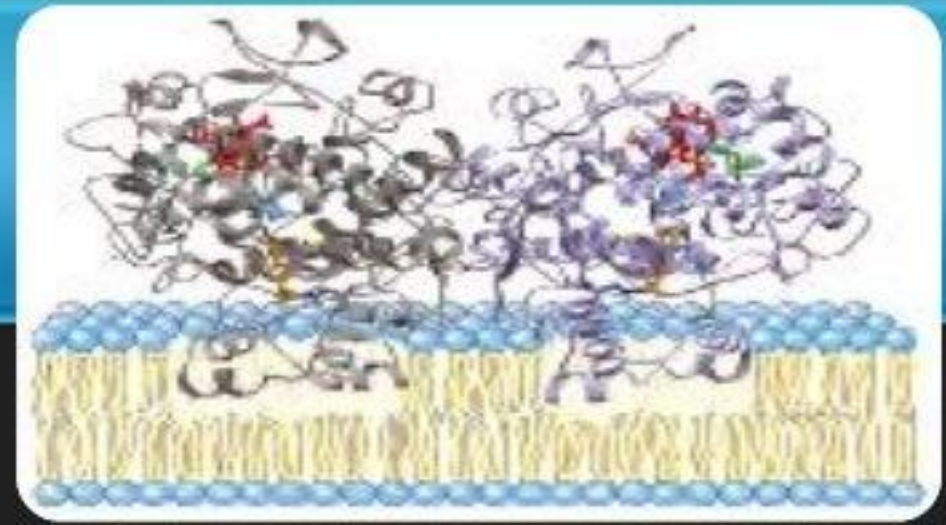
- ❖ Cytosol
- ❖ Requires NADPH
- ❖ Acyl carrier protein
- ❖ D-isomer
- ❖  $\text{CO}_2$  activation
- ❖ Citrate ion
- ❖ Multi-enzyme complex
- ❖ 2 carbon units added, as 3 carbon malonyl CoA

## DEGRADATION

- ❖ Mitochondria
- ❖ NADH,  $\text{FADH}_2$
- ❖ CoA
- ❖ L-isomer
- ❖ No  $\text{CO}_2$
- ❖ No citrate
- ❖ Enzymes as independent proteins
- ❖ 2 carbon units split off as acetyl CoA

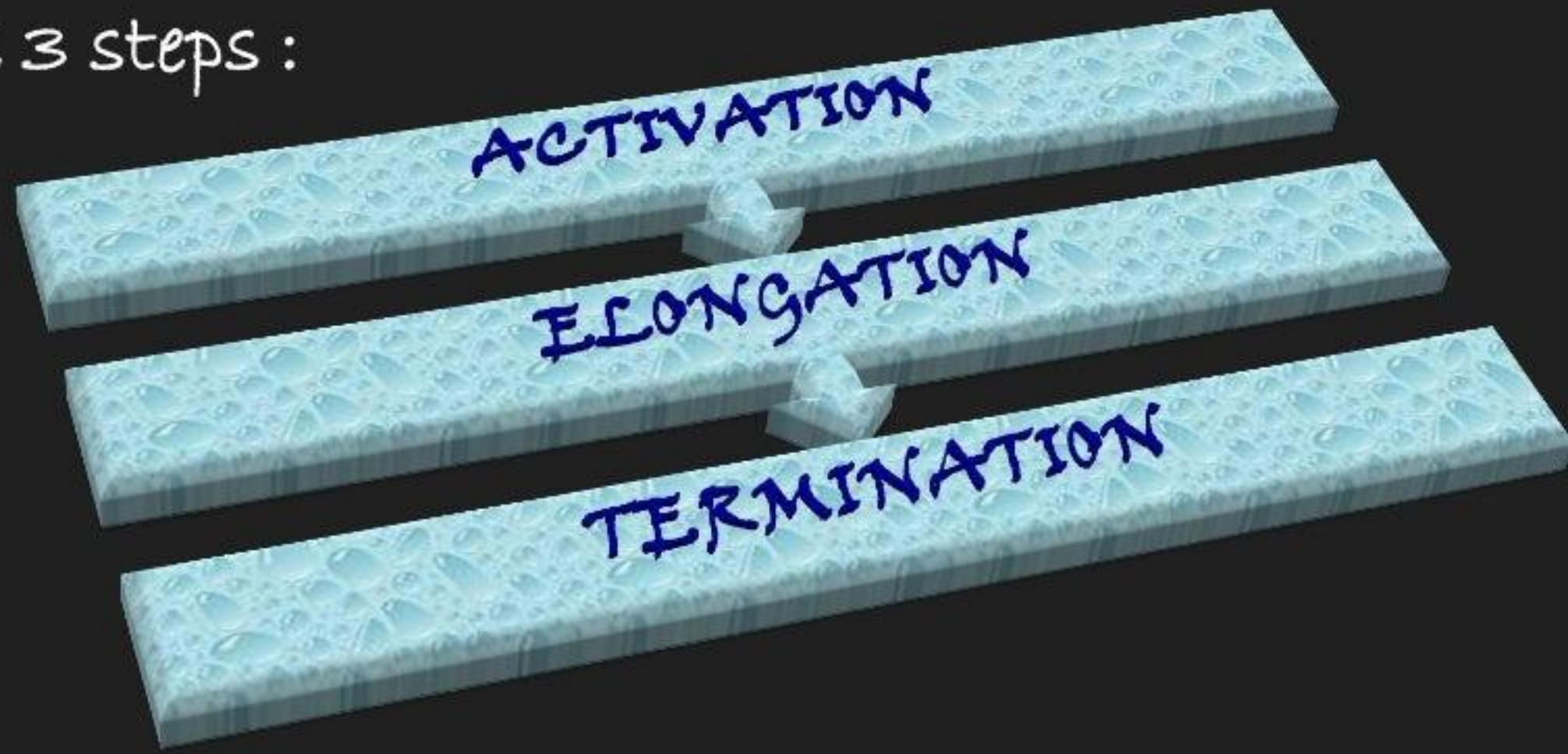


# Biosynthesis



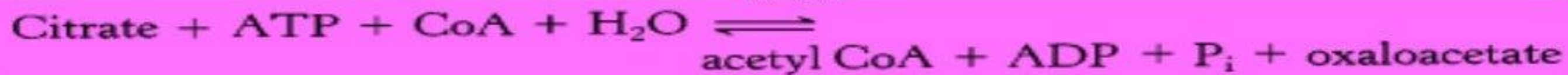
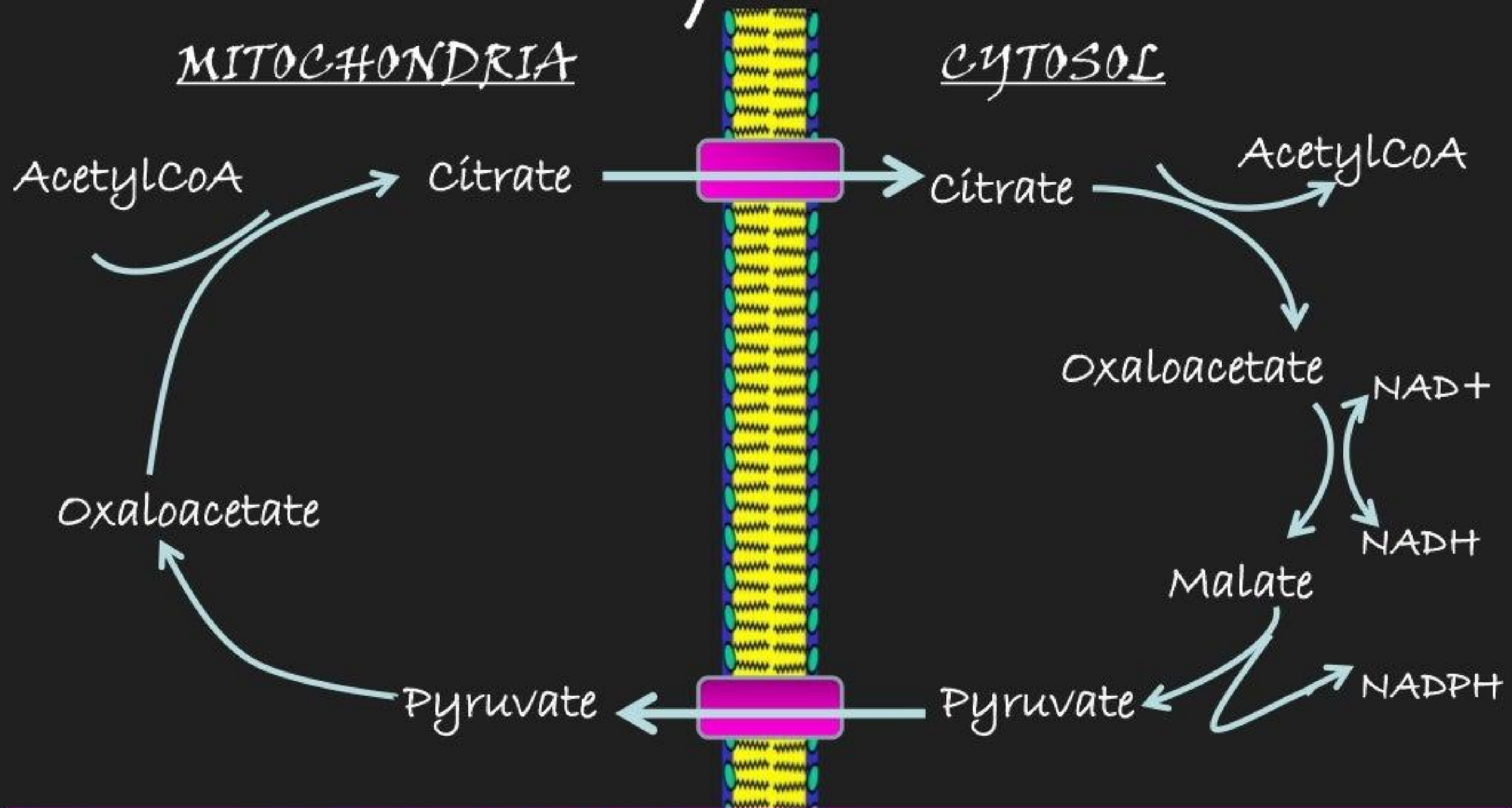
Fatty Acid biosynthesis is a stepwise assembly of acetyl-CoA units (in the form of malonyl-CoA units) ending with Palmitate (C-16).

It includes 3 steps :



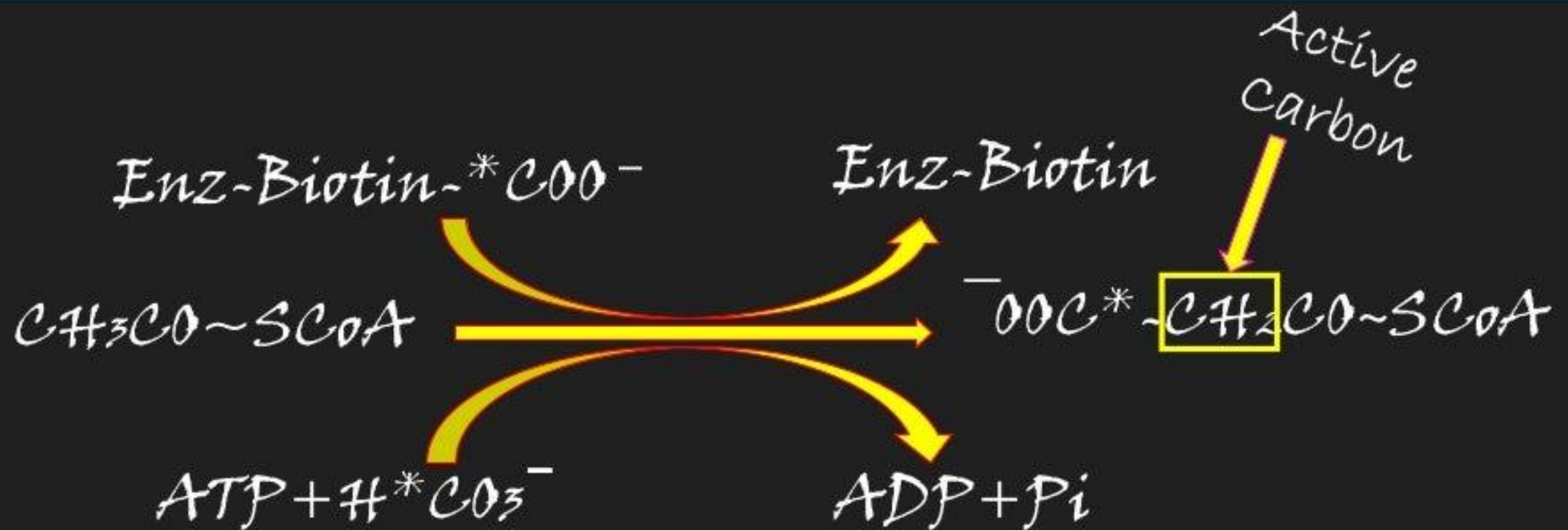


# Transfer of Acetyl CoA to Cytosol





# 1) Activation Of Acetyl-CoA



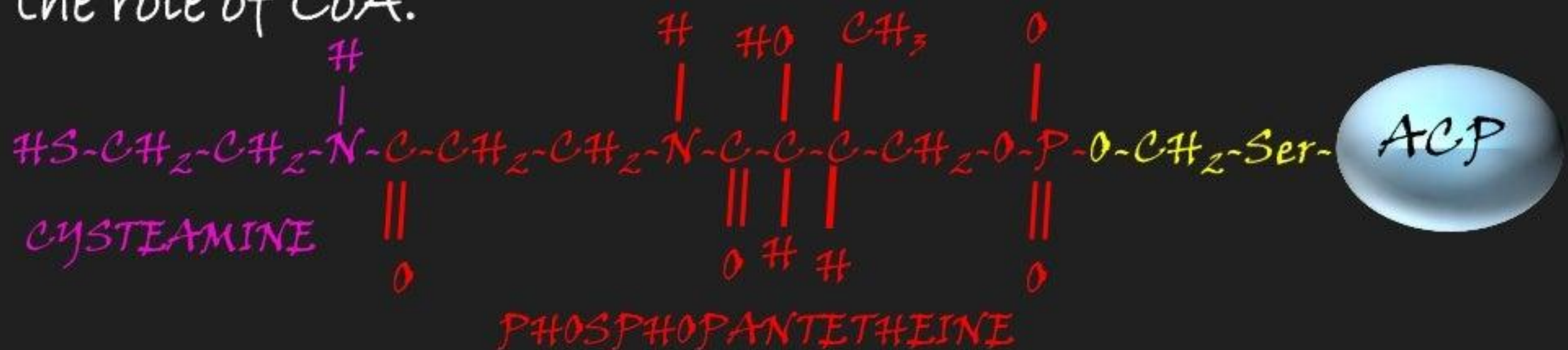
Reaction is catalyzed by acetyl-CoA carboxylase. It is a multienzyme protein. The enzyme contains a variable number of identical subunits, each containing biotin, biotin carboxylase, biotin carboxyl carrier protein, and transcarboxylase, as well as a regulatory allosteric site.



## 2) Elongation Cycle

The enzyme system that catalyzes the synthesis of saturated long-chain fatty acids from acetyl CoA, malonyl CoA, and NADPH is called the **fatty acid synthase**.

**Acyl Carrier Protein** contains the vitamin pantothenic acid in the form of 4'-phosphopantetheine. ACP takes over the role of CoA.



ACP, a single polypeptide chain of 77 residues, can be regarded as a giant prosthetic group.



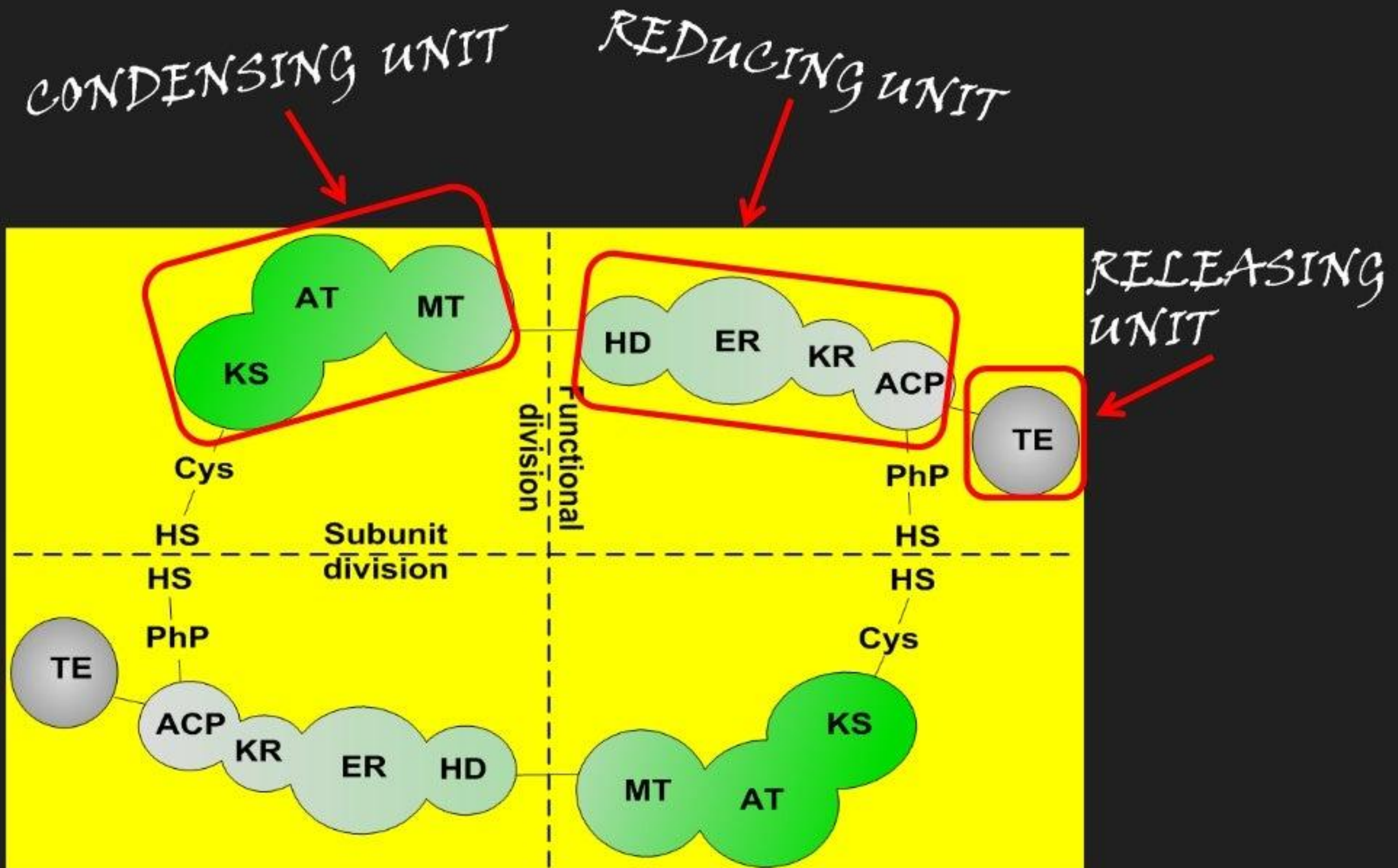
The elongation phase of fatty acid synthesis starts with the formation of acetyl ACP and malonyl ACP. Acetyl transacylase and malonyl transacylase catalyze these reactions.



The equilibrium is favorable if malonyl ACP is a reactant because its decarboxylation contributes a substantial decrease in free energy.



## Fatty Acid Synthase Complex





# 7 Enzymes for 7 Reactions!!!

1. Acetyl-CoA-ACP transacylase: The acetyl group of acetyl-CoA is transferred to a cysteine thiol on the  $\beta$ -ketoacyl-ACP synthase domain.
2. Malonyl-CoA-ACP transacylase: The malonyl group of malonyl-CoA is transferred to ACP (acyl carrier protein), to which it is attached via phosphopantetheine (i.e. same linkage as in CoA).
3.  $\beta$ -ketoacyl-ACP synthase: acetyl-ACP and malonyl-ACP condense together, releasing  $\text{CO}_2$ , to form  $\beta$ -ketoacyl-ACP. The acyl chain is now on ACP, where it will stay for the remainder of the reactions in this cycle.



4.  $\beta$ -ketoacyl-ACP reductase: Using NADPH, the ketone is reduced to a hydroxyl group. (Note that the carbon bearing the hydroxyl is chiral – this compound is in the D-configuration.)
5.  $\beta$ -hydroxyacyl-ACP dehydratase: Water is eliminated, making a trans- $\Delta^2$ -enoyl-ACP.
6. enoyl-ACP reductase: Using NADPH, the double bond is saturated.



7 iterations of this cycle will give a Palmitoyl- ACP.



# ELONGATION

$\beta$ -Carbon

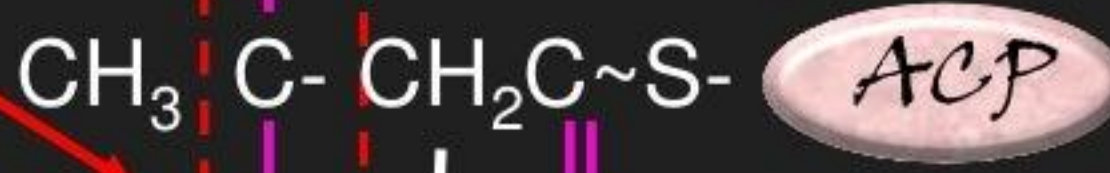


NADPH

REDUCTION



Disomer



DEHYDRATION

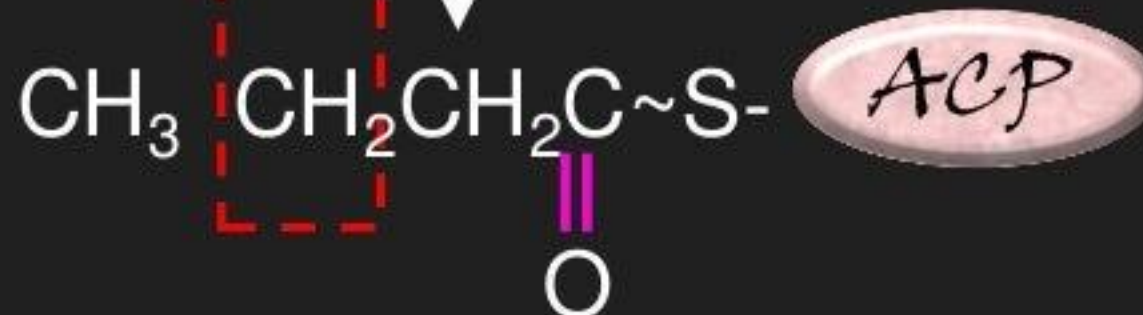
$-\text{H}_2\text{O}$



NADPH



REDUCTION

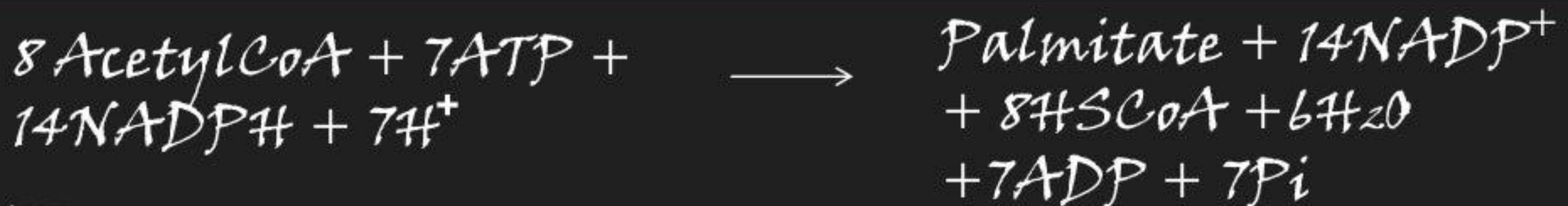




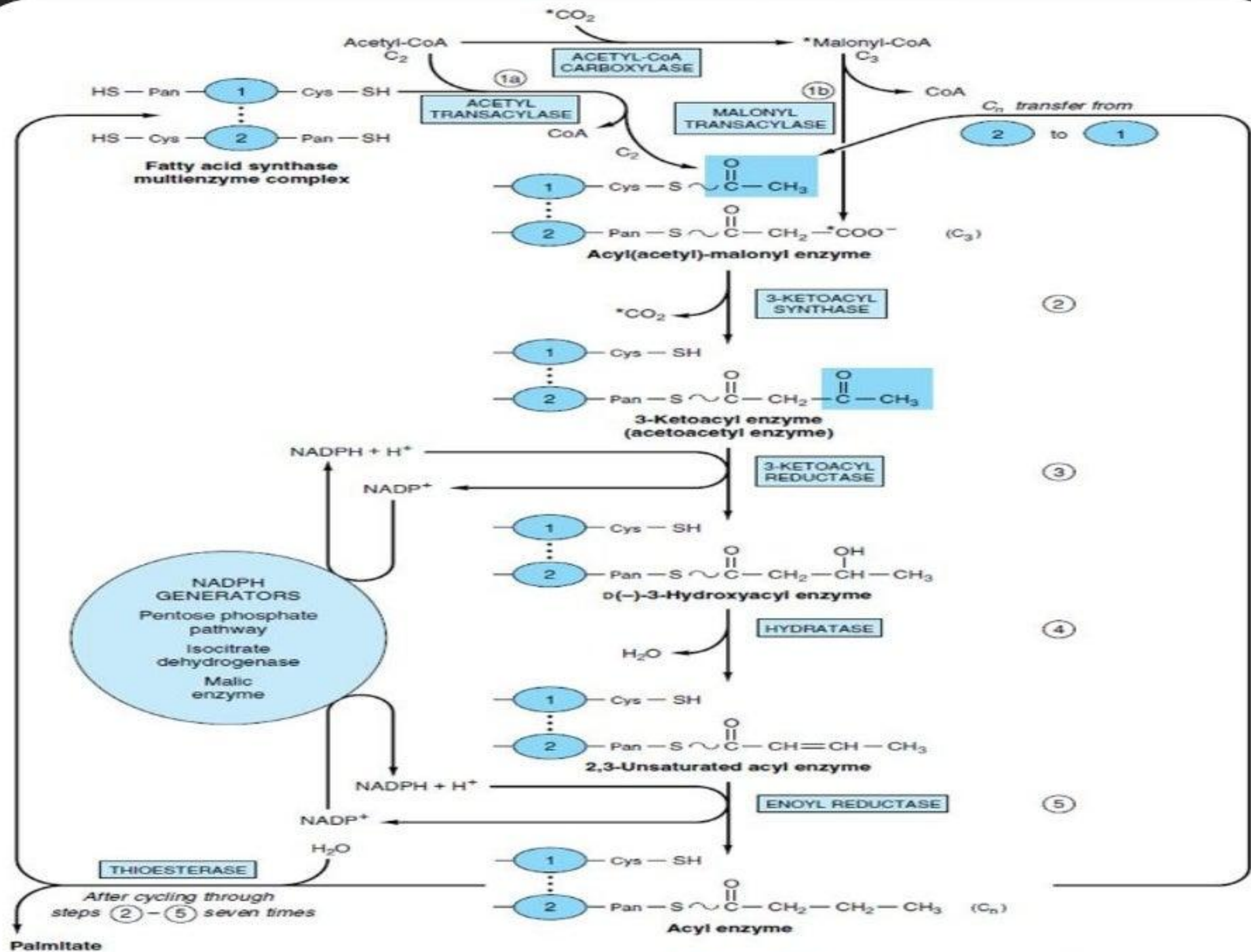
# Termination via 7th Enzyme

7. thioesterase: Palmitate is released by hydrolysis of palmitoyl-ACP via thioesterase. This enzyme is rather specific for C16.

## Reactions









# Post Synthesis Modification

## 1) ELONGATION

Elongation beyond the 16-C length of the palmitate product of Fatty Acid Synthase is mainly catalyzed by enzymes associated with the endoplasmic reticulum (ER).

ER enzymes lengthen fatty acids produced by Fatty Acyl Synthase as well as dietary polyunsaturated fatty acids.

Fatty acids esterified to coenzyme A serve as substrates.

Malonyl-CoA is the donor of 2-carbon units in a reaction sequence similar to that of Fatty Acid Synthase except that individual steps are catalyzed by separate proteins.



## 2) UNSATURATION

Desaturase introduce double bonds at specific positions in a fatty acid chain.

Mammalian cells are unable to produce double bonds at certain locations, e.g.,  $\Delta^{12}$ . Thus some polyunsaturated fatty acids are dietary essentials, e.g., linoleic acid.

In the conversion of stearoyl CoA into oleoyl CoA, a *cis*- $\Delta^9$  double bond is inserted by an oxidase that employs molecular oxygen and NADH (or NADPH).





# Membrane Bound Enzymes Present in E.R

Formation of a double bond in a fatty acid involves the following endoplasmic reticulum membrane proteins in mammalian cells.

NADH-  
CYTOCHROME  
-B5  
REDUCTASE

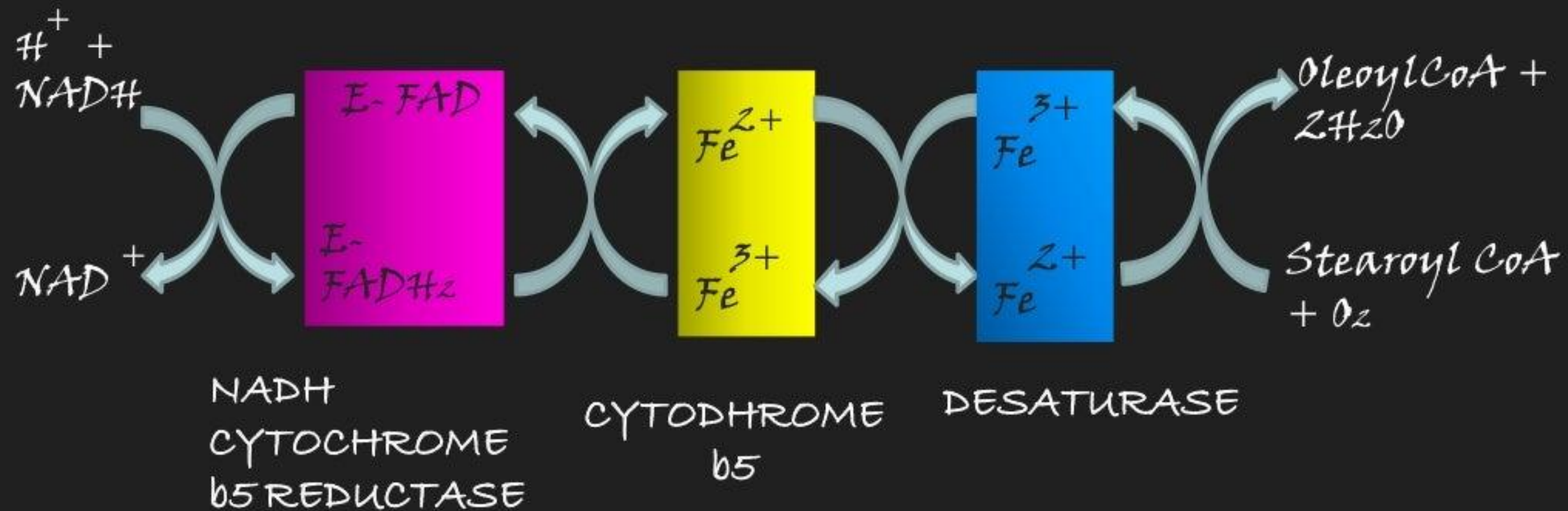
CYTOCHROME  
-B5

DESATURASE

First, electrons are transferred from NADH to the FAD moiety of NADH-cytochrome b 5 reductase .

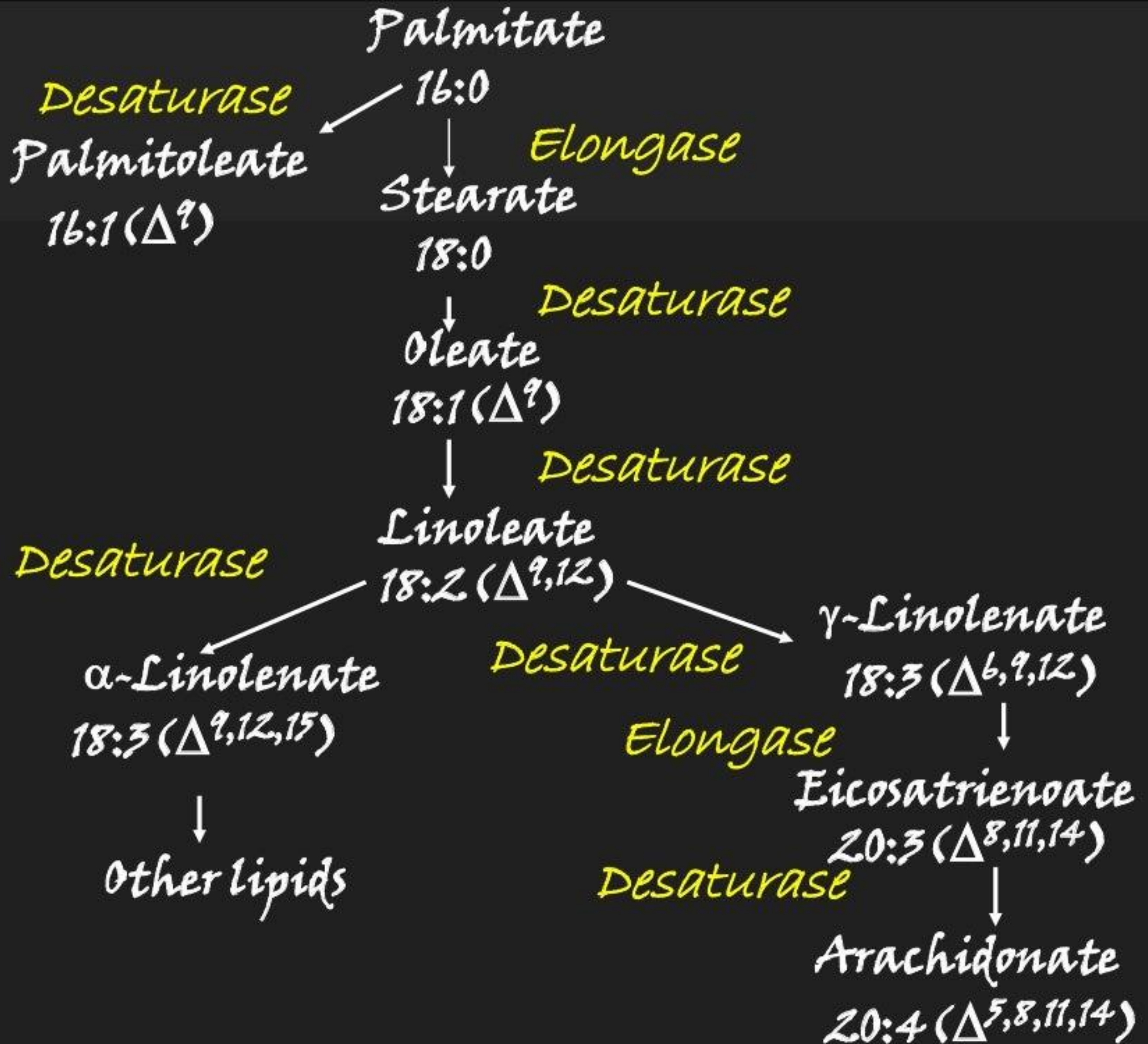


# Electron Transport Chain In The Desaturation Of Fatty Acids



The nonheme iron atom of the desaturase is subsequently converted into the  $Fe^{+3}$  state, which enables it to interact with  $O_2$  and the saturated fatty acyl CoA substrate. Two electrons come from NADH and two from the single bond of the fatty acyl substrate.







# REFERENCES

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- ✓ Biochemistry\_Lehninger
- ✓ Harper's Illustrated Biochemistry (26<sup>th</sup> ed)
- ✓ Biochemistry of fatty acids- Medical biochemistry
- ✓ Fatty Acid Synthesis- Renesselear