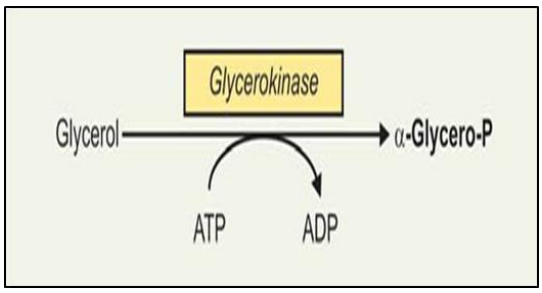
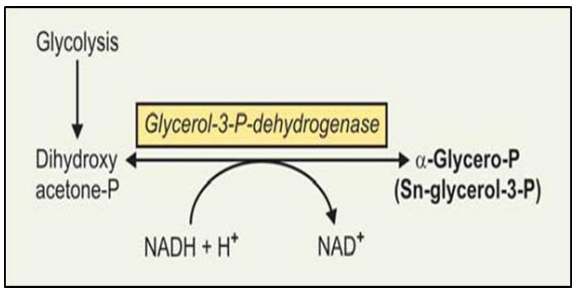
Lipogenesis

Def:	• *Biosynthesis of **triacylglycerol from excess glucose** after a carbohydrate rich meal.*
Site:	• *Occurs in **most tissues** especially liver and adipose tissue*
Substrates:	• *Glycerol-3-P (**glycerol-3-P**)* • ***Fatty acid** (Acyl-CoA)*
Steps:	***1) Synthesis of Glycerol-3-P:*** ***a) Phosphorylation of glycerol:*** ➢ *This reaction is mediated by **glycerokinase enzyme** in presence of ATP.* ➢ *Glycerokinase enzyme is **absent or very low in activity in muscle and adipose tissue.*** ***b) Dihydroxyacetone-phosphate (DHAP):*** ➢ *DHAP is considered an **alternative source of glycerol-3-P** in muscle and adipose tissue, **where glycerokinase is lacking.*** ➢ *DHAP is an intermediate of glycolysis.* ➢ *DHAP is reduced to Glycerol-3-P by the enzyme **Glycerol-3-P dehydrogenase** in presence of NADH+H.*  

2) Synthesis of Fatty acids:

- ***There are three systems for fatty acid synthesis:***

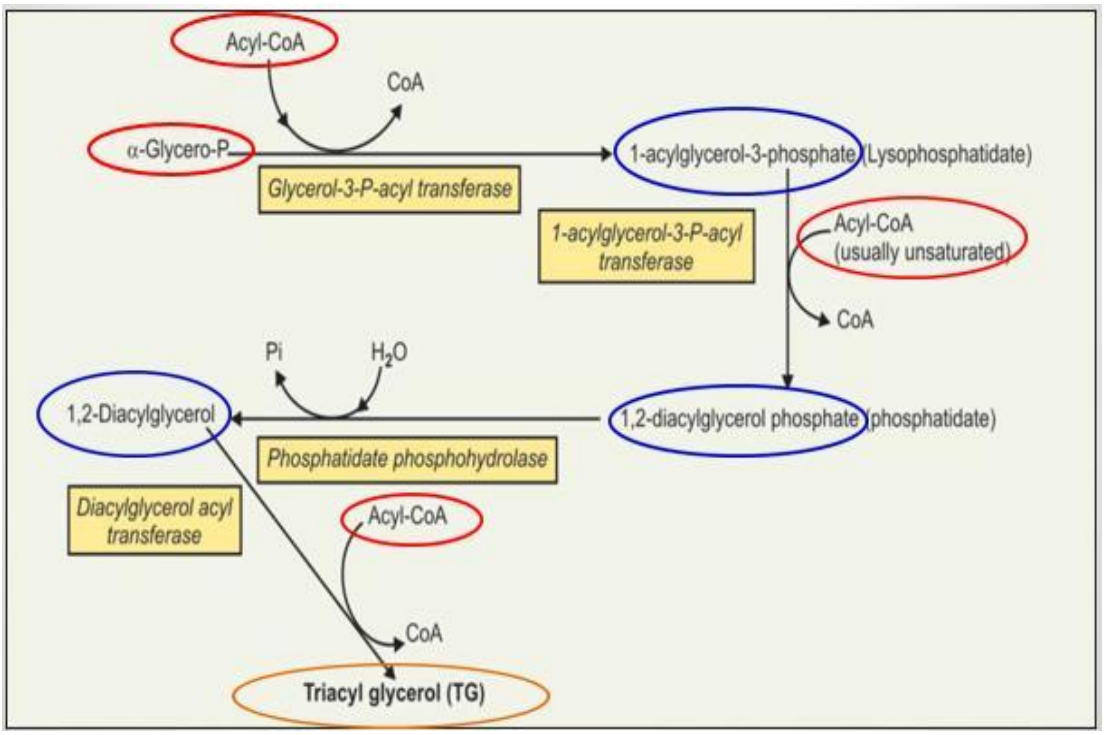
  A. Extramitochondrial (Cytoplasmic) system.

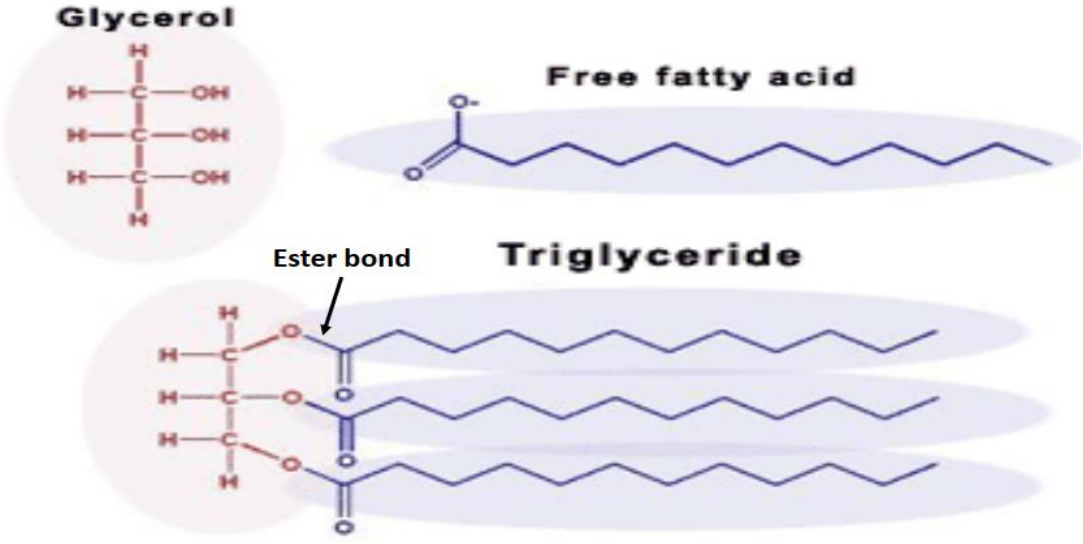
  B. Chain Elongation System:

  a) Microsomal system.

  b) Mitochondrial system.

3) Synthesis of Triacylglycerol:





Extramitochondrial (Cytoplasmic) system

Definition:	• *It is the system responsible for **de novo synthesis** of FA from acetyl-CoA.*	
Site:	• ***Cytosol of** Liver, adipose tissue, kidney, brain, and mammary glands.*	
End product:	• *Synthesis always ends in formation of **palmitic acid.***	
Materials required for the synthesis:	• ***Acetyl CoA** is the starting material for de novo synthesis of Fatty acids.* • ***NADPH+H.***	
Enzymes of extra-mitochondrial Pathway:	• *Fatty acid synthase complex.* • *Acetyl-CoA carboxylase enzyme.*	
Acetyl CoA sources and fates	**Sources of Acetyl CoA**	**Fates of Acetyl CoA**
	1. *Metabolism of **glucose.*** 2. *β-oxidation of **FA.*** 3. *Catabolism of **Ketogenic amino acids.*** **4. *ketolysis.*** 5. ***Acetate** by Acetyl-CoA-Synthase.*	1. *Principal fate is oxidation in **TCA cycle.*** 2. ***Fatty acid and cholesterol** biosynthesis.* **3. *Ketogenesis.*** 4. *Formation of **acetylcholine.*** 5. *Acetylation reactions (Detoxication).*

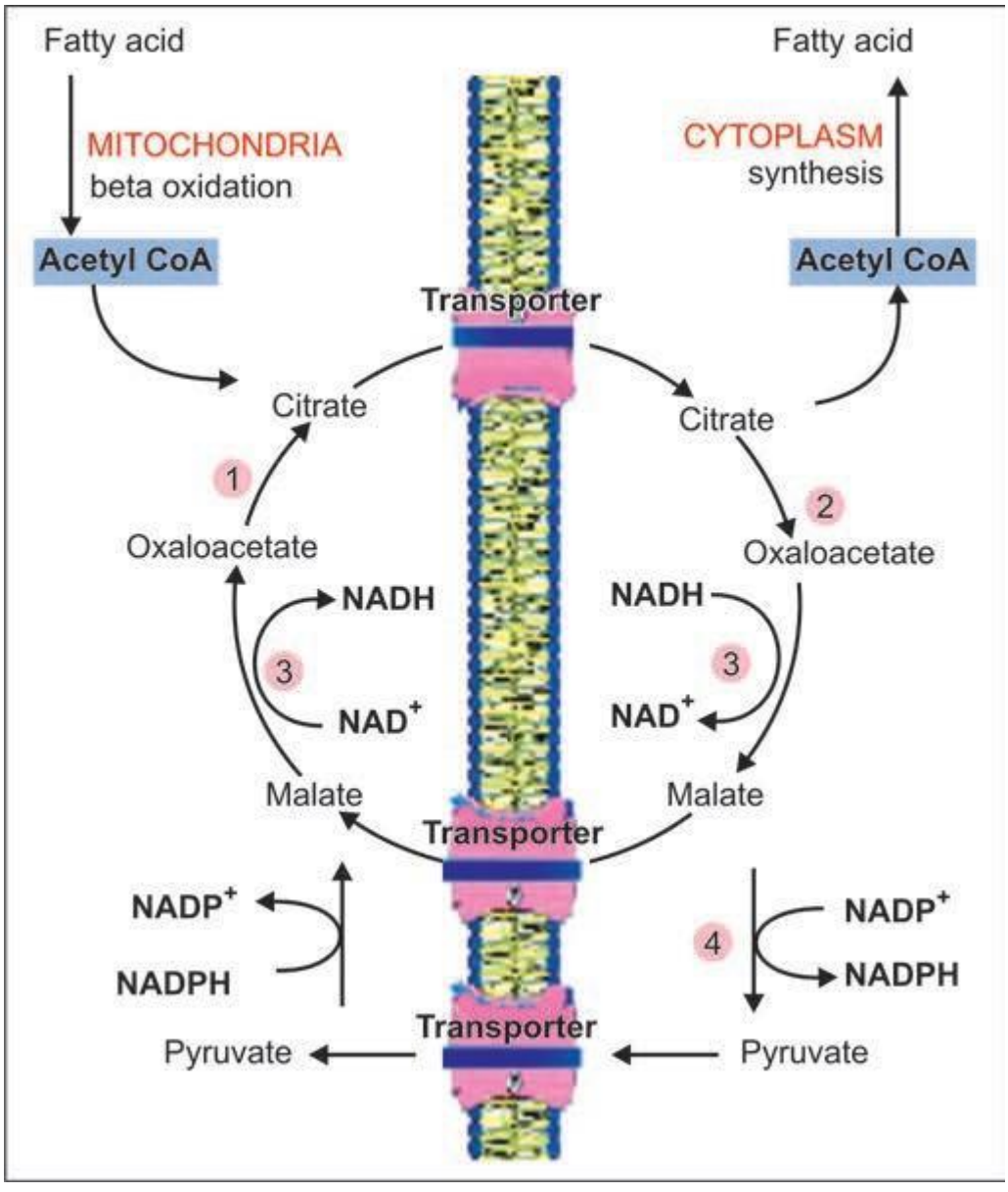
- ***Translocation of Acetyl-CoA from mitochondria to cytoplasm:***
  - *Acetyl CoA is formed in mitochondrion but FA synthesis occurs in cytosol.*
  - ***The mitochondrial membrane is impermeable to acetyl CoA.***

    1) Acetyl CoA condenses with oxaloacetic acid by citrate synthetase *to form citrate which can pass out mitochondrial membrane by a transporter.*

    2) *In the cytoplasm, citrate is cleaved to oxaloacetate and acetyl CoA by* ***ATP-citrate lyase.***

    3) *Oxaloacetate is converted to malate by* ***malate dehydrogenase.***

    4) *Malate may be returned to the mitochondria by a transporter or may be converted into pyruvate by* ***malic enzyme*** *and the produced NADPH+H+ is used for FA synthesis.*



- **Sources of NADPH:**

1) Hexose monophosphate shunt (HMP) pathway:

- *It is the main source of NADPH+H.*

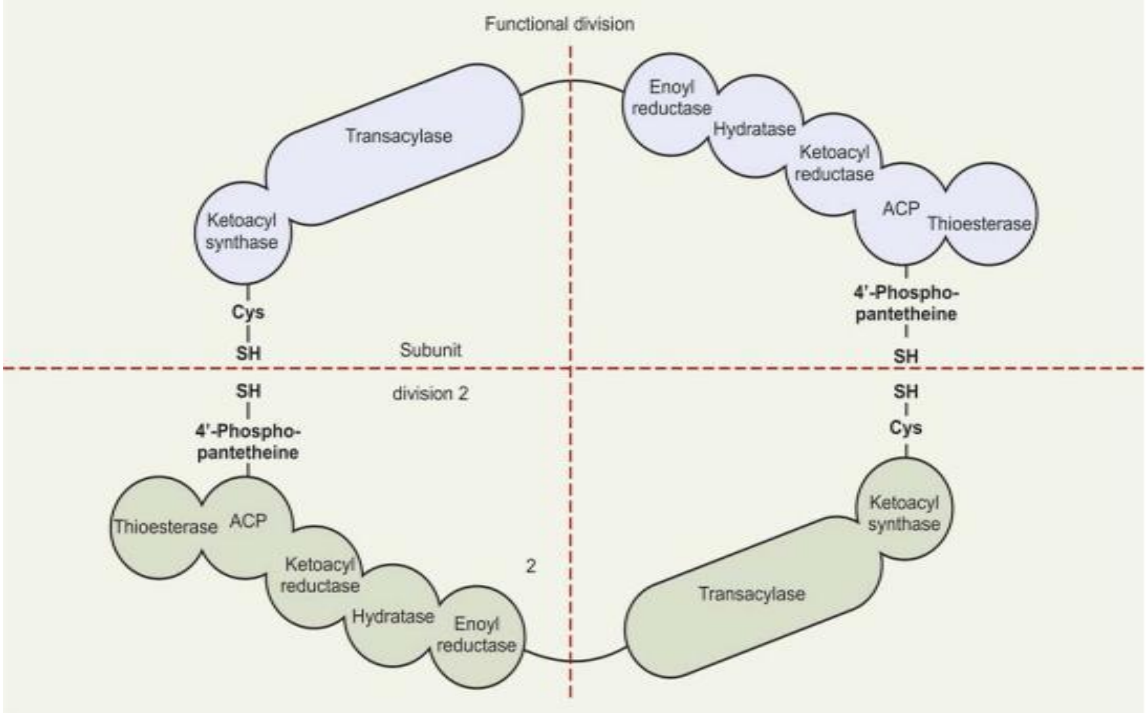
2) Cytoplasmic malic enzyme (NADP-malate dehydrogenase):

- *Malate + NADP+ → Pyruvate + CO2 + NADPH + H+*

3) Cytoplasmic isocitrate dehydrogenase enzyme.

- **Structure of fatty acid synthase complex:**

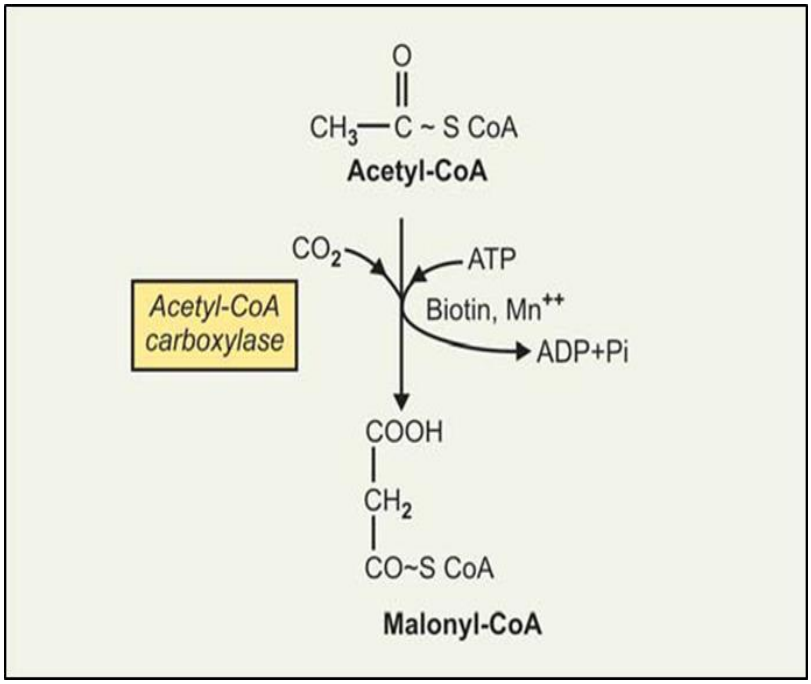
- *Fatty acid synthase complex is a* ***multienzyme complex.***
- *It is made up of dimer of* ***two identical monomeric*** *units, arranged in a* ***head to tail fashion.***
- *Each monomeric unit contains* ***six enzymes and an ACP molecule*** *(Acyl carrier protein).*
- *ACP contains* ***pantothenic acid (Vit B5)*** *containing* ***SH group*** *referred as* ***Pantothenyl-SH (Pan-SH).***
- *In close proximity is another SH group of* ***β-ketoacyl synthase*** *(condensing enzyme) of the other monomer referred as Cysteinyl-SH (Cys–SH).*
- *Since both SH group participate in the synthase activity,* ***only the dimer is active.***



Steps of extra-mitochondrial pathway

1. Formation of malonyl CoA by acetyl-CoA carboxylase:

- *Acetyl-CoA is converted to **malonyl-CoA** in the presence of ATP, biotin and bicarbonate as a source of CO2*



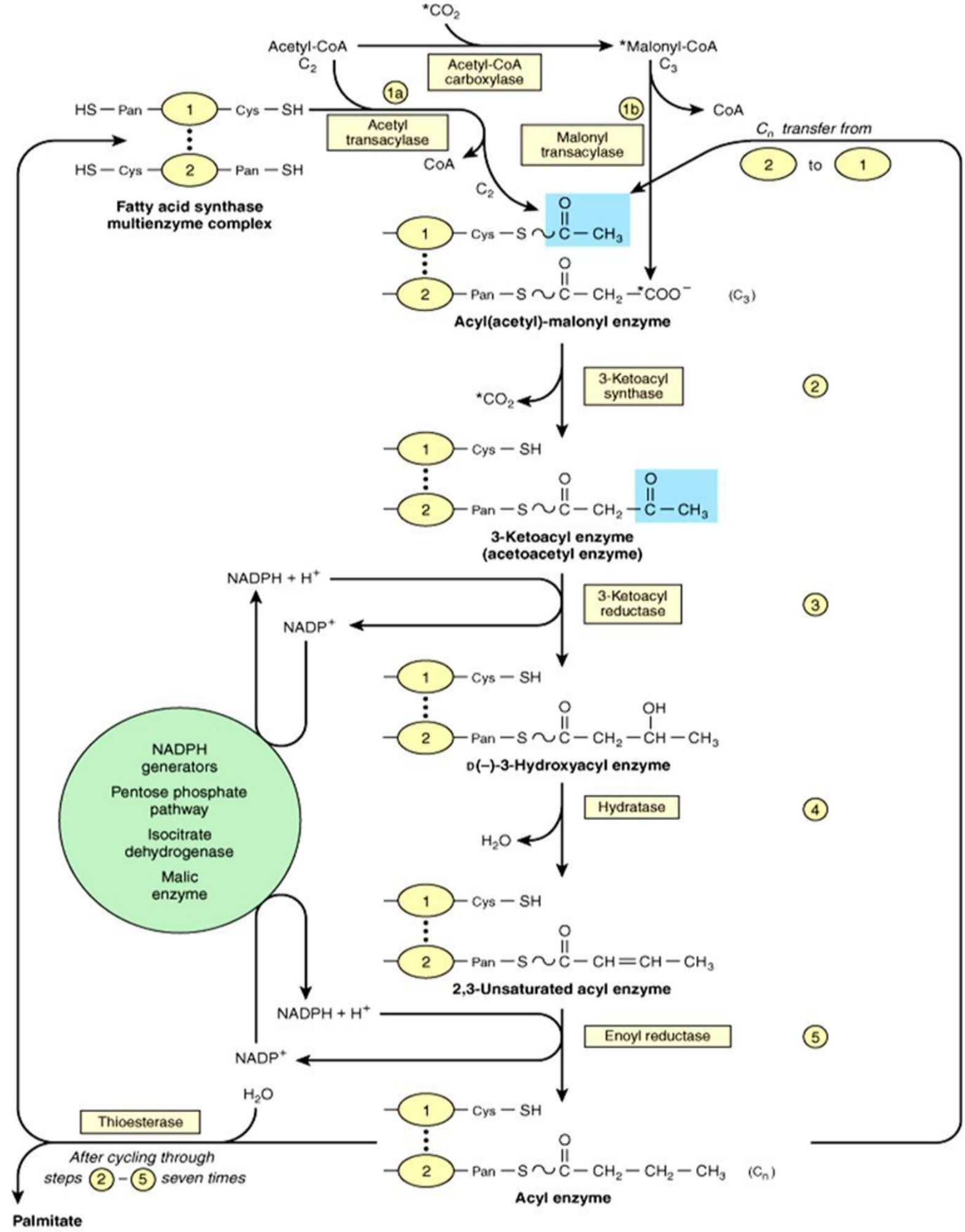
2. Synthesis of palmitate by the fatty acid synthase complex:

Step 1:	• **Acetyl group and malonyl group are Added to the enzyme complex:** ➢ **Step 1a:** *The **acetyl transacylase** transfers the acetyl group to the "Cys-SH" of "keto acyl synthase" of one monomeric unit (**Monomer I**).* ➢ **Step 1b:** *The **malonyl transacylase** transfers the malonyl group to the adjacent "Pan SH" of ACP of opposite monomeric unit (**Monomer II**).*
Step 2:	• **Condensation:** ➢ *The acetate attacks malonate to form **aceto-acetyl-ACP (3 keto acyl ACP)** by **3-Keto-acyl synthase (condensing) enzyme** with loss of CO2.*

Step 3:	• ***Reduction:*** ➢ *The 3-keto acyl ACP is reduced by NADPH dependent* ***3-keto acyl reductase*** *to 3 hydroxy acyl ACP.*
Step 4:	• ***Dehydration:*** ➢ *The 3-hydroxy acyl ACP is dehydrated by* ***a dehydratase*** *to form enoyl ACP (alpha beta unsaturated acyl ACP).*
Step 5:	• ***Reduction:*** ➢ *The enoyl ACP is reduced by* ***enoyl reductase*** *utilizing a 2nd molecule of NADPH to form butyryl ACP.*

NB:

- ***Transfer*** *of butyryl group* ***from monomer 2 to 1.***
- ***Now position 2 is free*** *to accept a new malonyl CoA.*
- *The sequence of reactions (steps 2-5) are* ***repeated*** *till the palmitic acid is formed.*
- *Palmitic acid is released from the enzyme complex by* ***the thio-esterase.***


*CO2
Acetyl-CoA
C2
Acetyl-CoA carboxylase
*Malonyl-CoA
C3
1a
1b
CoA
HS — Pan — 1 — Cys — SH
HS — Cys — 2 — Pan — SH
Acetyl transacylase
Malonyl transacylase
Cn transfer from
2 to 1
Fatty acid synthase multienzyme complex
C2
1 — Cys — S — C(=O) — CH3
2 — Pan — S — C(=O) — CH2 — *COO−
(C3)
Acyl(acetyl)-malonyl enzyme
*CO2
3-Ketoacyl synthase
2
1 — Cys — SH
2 — Pan — S — C(=O) — CH2 — C(=O) — CH3
3-Ketoacyl enzyme (acetoacetyl enzyme)
NADPH + H+
NADP+
3-Ketoacyl reductase
3
1 — Cys — SH
2 — Pan — S — C(=O) — CH2 — CH(OH) — CH3
D(−)-3-Hydroxyacyl enzyme
NADPH generators
Pentose phosphate pathway
Isocitrate dehydrogenase
Malic enzyme
Hydratase
4
H2O
1 — Cys — SH
2 — Pan — S — C(=O) — CH=CH — CH3
2,3-Unsaturated acyl enzyme
NADPH + H+
NADP+
Enoyl reductase
5
H2O
Thioesterase
1 — Cys — SH
2 — Pan — S — C(=O) — CH2 — CH2 — CH3
(Cn)
Acyl enzyme
After cycling through steps 2 – 5 seven times
Palmitate

Regulation of FA synthesis:

- ***Acetyl CoA carboxylase*** *is the most important enzyme in the regulation of FA synthesis.*
- ***<u>It is regulated by:</u>***

1) Phosphorylation (covalent modification):	• *Insulin* ***activates*** *it by dephosphorylation.* • *Glucagon and epinephrin* ***inactivates*** *it by phosphorylation.*
2) Allosteric regulation:	• *It is an* ***allosteric enzyme*** *is activated by citrate and inhibited by long chain FA.*
3) Long term regulation:	• *The amount of the enzyme increases in* ***fed state*** *and decrease in* ***high fat diet intake and starvation.***

Fates of palmitic acid:

- ***Palmitic acid*** *must be activated to* ***palmitoyl CoA*** *before it proceeds via any other pathway as:*

1. Synthesis of other fatty acids:	• *Longer chain FA by chain* ***elongation.*** • *Unsaturated FA by* ***desaturation.***
2. Esterification:	• *Esterification with glycerol or with cholesterol to form* ***TG*** *or* ***cholesterol ester*** *respectively.*
3. Sphingosine formation	• *Sphingosine formation by binding to serine.*

Clinical Correlation:

- ***Pantothenic Acid (B5) is Clinically Relevant For:***
  - *Supporting healthy synthesis of lipids and essential fatty acids.*
  - *Pantothenic acid is converted into 4'-phosphopantetheine that is* ***integral part of the acylation carriers, CoA and acyl carrier protein (ACP).***
  - *Acne results from a reduced efficiency in lipid metabolism, via coenzyme A, that is secondary to a deficiency in pantothenic acid.*