Lipids

3rd Stage
Asst. Lec. Zainab AL-Shoroofi
M.Sc. in Chemistry Sciences

Metabolism

- Definition of metabolism
- Classification of metabolism

Metabolism of Lipids

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Zainab AL-Shoroofi

METABOLISM

Metabolism means the series of biochemical reactions that occur for biomolecules in living organisms.

It is classified into: anabolism and catabolism.

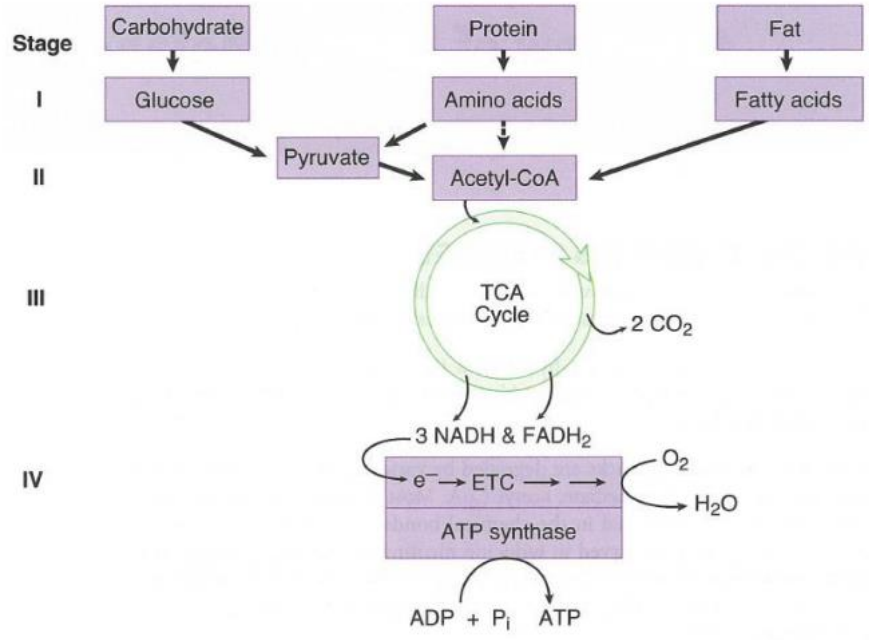
Anabolism: Means synthesis of macromolecules from simple one. Anabolism is usually endergonic (consumes energy).

Examples:

- Synthesis of polysaccharides from monosaccharides.
- Synthesis of triacylglycerol from glycerol and fatty acids.
- Synthesis of proteins from amino acids.

Catabolism: Means breakdown of macromolecules into simplest components. It is usually exergonic (release energy).

Catabolism of the main metabolites occurs in 4 stages: **(Figure 1)**



(Figure 1)

Metabolism of Lipids:

1. Synthesis of fatty acids

Site: Liver, kidney, brain, mammary gland, adipose tissue.

Cellular site: Cytosol.

Coenzymes/cofactors: NADPH.

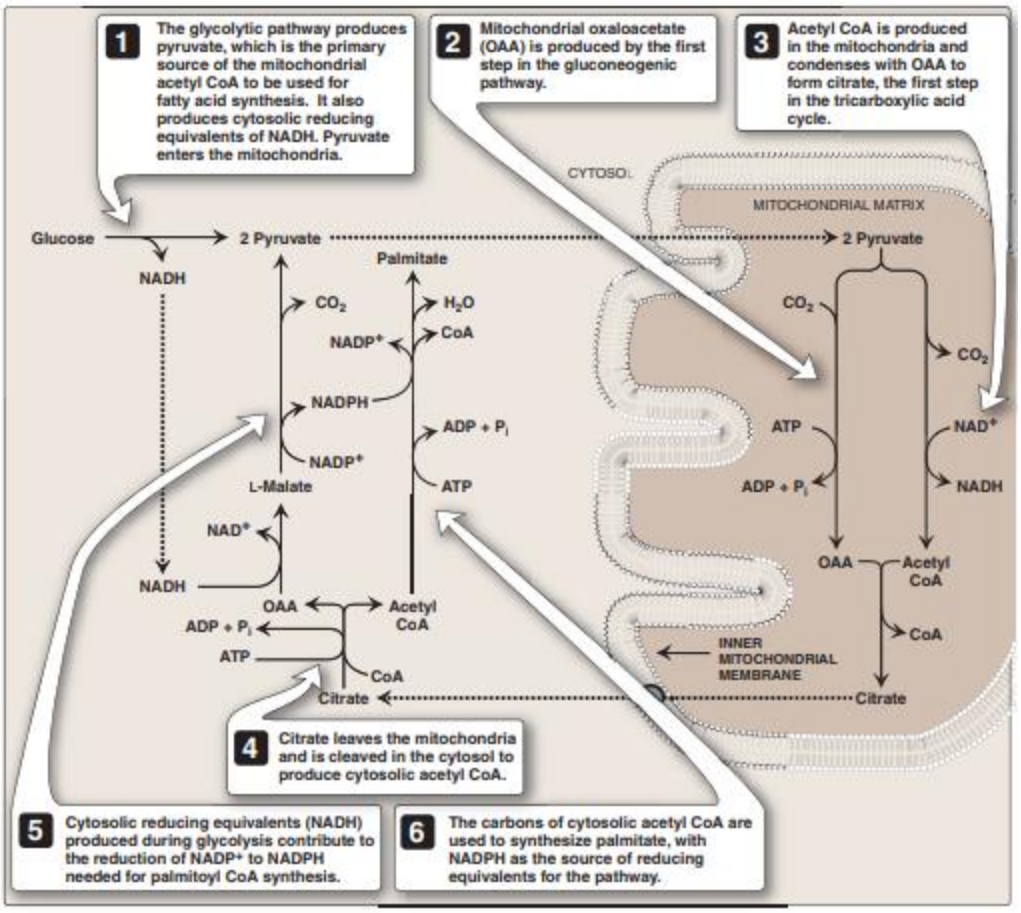
Starting material: Acetyl-CoA.

End product: Palmitate.

Steps in the synthesis of fatty acids

Transport of acetyl-CoA from mitochondria to cytosol (as citrate)

Role of citrate: acetyl-CoA is formed by pyruvate in the mitochondria and transferred to the site of synthesis (cytosol) after getting converted into citrate **(Figure 2).**



(Figure 2)

[1] An acetyl group is transferred from acetyl CoA to the -SH group of the ACP. (Acetyl CoA-ACP acetyltransacylase).

[2] Next, this two-carbon fragment is transferred to a temporary holding site, the thiol group of cysteine residue on the enzyme.

[3] The now-vacant ACP accepts a three-carbon malonyl group from malonyl CoA. (Malonyl CoA-ACP transacylase).

[4] The acetyl group on the cysteine residue condenses with the malonyl group on ACP, and the CO_2 is released. The result is a four-carbon unit attached to the ACP domain. (3-ketoacyl-ACP synthase).

The next three reactions convert the 3-ketoacyl group to the corresponding saturated acyl group by a pair of NADPH-requiring reductions and a dehydration step.

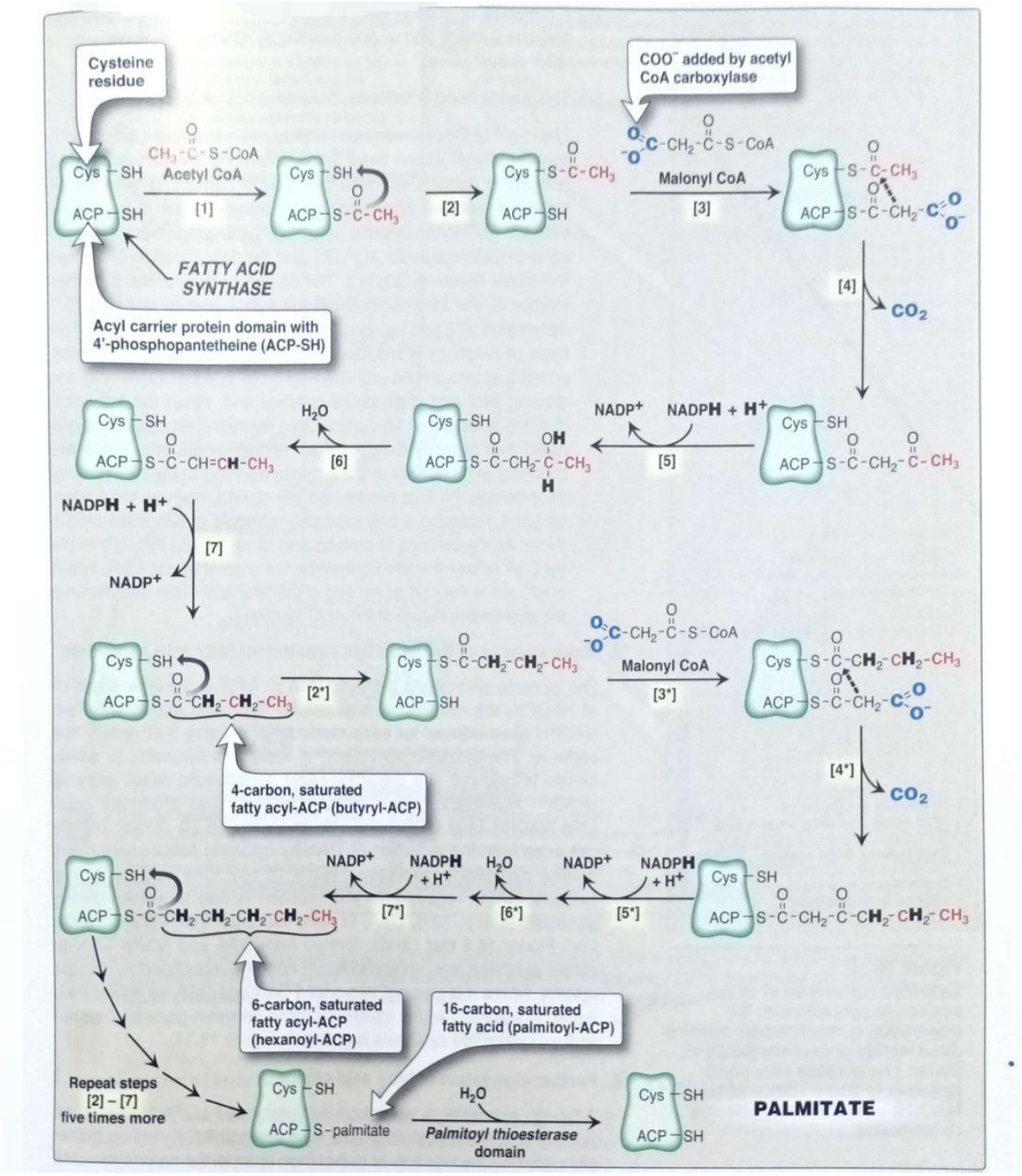
[5] The keto group is reduced to an alcohol. (3-ketoacyl-ACP reductase)

[6] A molecule of water is removed, creating a double bond between carbon 2 and 3 (the α- and β-carbons). (3-Hydroxyacyl-ACP dehydratase).

[7] the double bond is reduced. (Enoyl-ACP reductase).

The result of these seven steps is production of a four-carbon compound (butyryl) whose three terminal carbons are fully saturated, and which remains attached to the ACP domain. These seven steps are repeated, beginning with the transfer of the butyryl chain from the ACP to the cysteine residue [2*], the attachment of a molecule of malonate to the ACP [3*], and the condensation of the two molecules liberating CO_2 [4*]. The carbonyl group at the β-carbon (carbon 3, the third carbon from the sulfur) is then reduced [5*], dehydrated [6*], and reduced [7*], generating hexanoyl-ACP.

This cycle of reactions is repeated five more times, each time incorporating a two-carbon unit (derived from malonyl CoA) in to the growing fatty acid chain at the carboxyl end. When the fatty acid reaches a length of 16 carbons, the synthetic process is terminated with palmitoyl-S-ACP. Palmitoyl thioesterase, the final catalytic activity of fatty acid synthase (FAS), cleaves the thioester bond, releasing a fully saturated molecule of palmitate. **(Figure 3).**


Cysteine residue
Acetyl CoA
[1]
[2]
COO⁻ added by acetyl CoA carboxylase
Malonyl CoA
[3]
FATTY ACID SYNTHASE
Acyl carrier protein domain with 4'-phosphopantetheine (ACP-SH)
[4]
CO2
NADP+
NADPH + H+
[5]
H2O
[6]
[7]
4-carbon, saturated fatty acyl-ACP (butyryl-ACP)
[2*]
Malonyl CoA
[3*]
[4*]
CO2
[5*]
[6*]
[7*]
6-carbon, saturated fatty acyl-ACP (hexanoyl-ACP)
16-carbon, saturated fatty acid (palmitoyl-ACP)
Repeat steps [2] – [7] five times more
Palmitoyl thioesterase domain
PALMITATE

(Figure 3)

2. β – Oxidation of fatty acids

Site: Mitochondria of all cells in the body.

Starting material: Fatty acids.

End products: Acetyl-CoA, NADH and $FADH_2$.

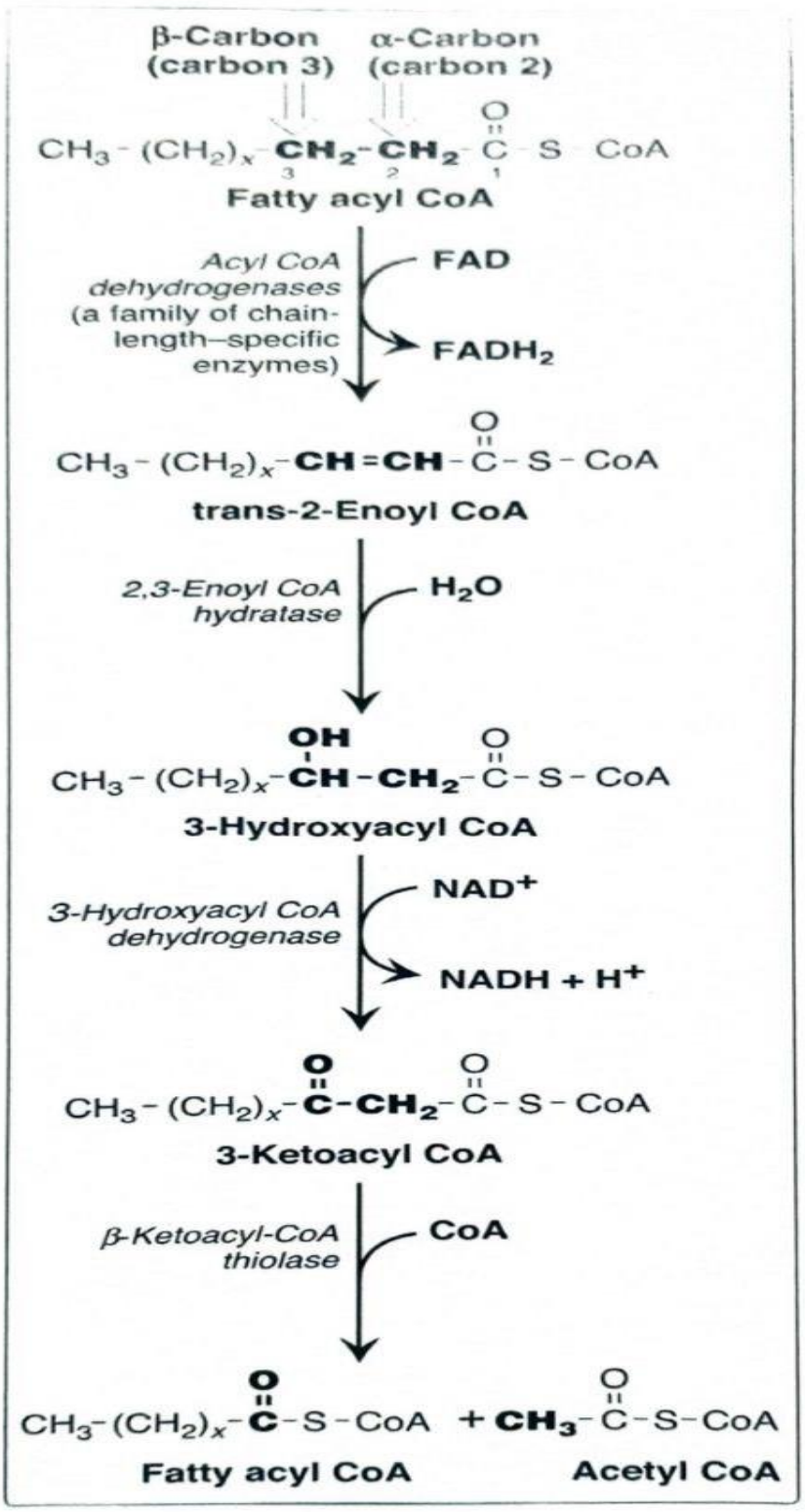
Coenzymes: NAD^+ and FAD.

Steps in β-oxidation of fatty acids

a. Activation of fatty acids into fatty acyl-CoA in the cytosol of cell.

b. Transport of fatty acyl-CoA from cytosol to mitochondria is carried out by carnitine shuttle. [Long-chain fatty acids (LCFA) cannot cross mitochondrial membrane; hence they need transport system. Carnitine transports LCFA through inner mitochondrial membrane].

c. β-oxidation involves four steps **(Figure 4)**
   - Oxidation
   - Hydration
   - Oxidation
   - Cleavage.

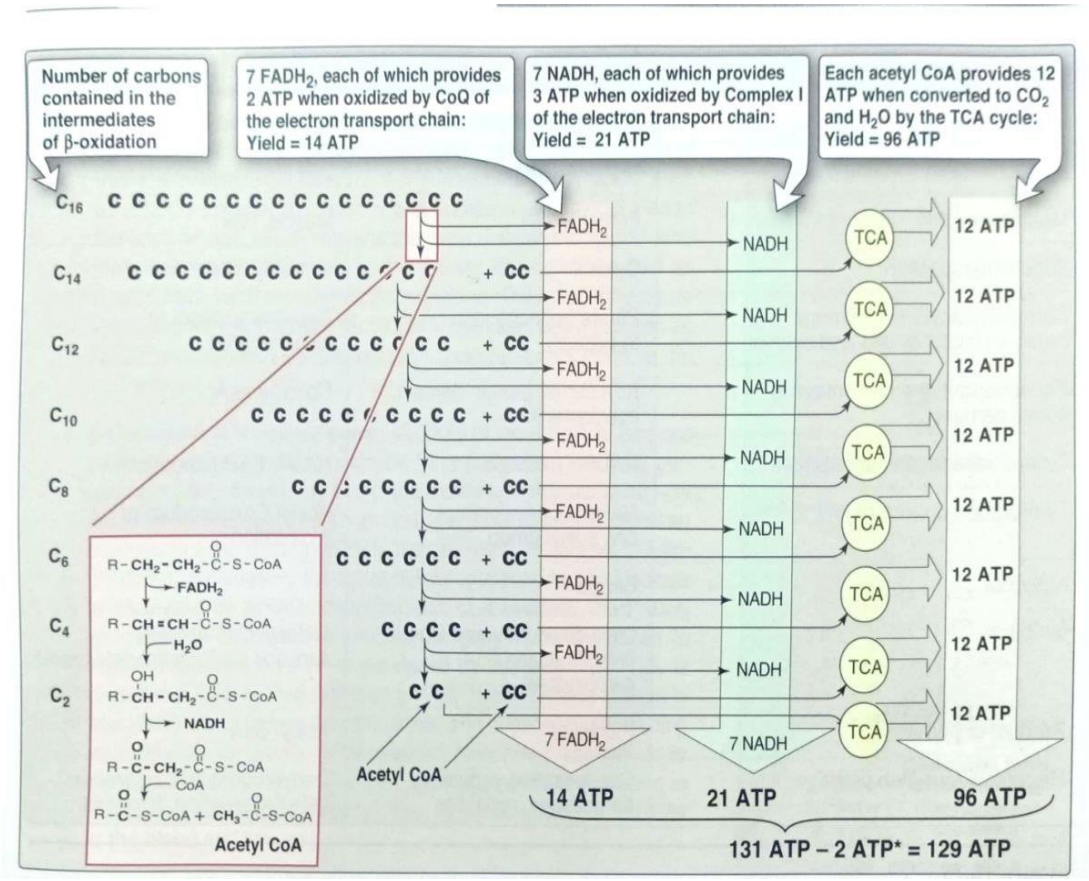

β-Carbon (carbon 3)
α-Carbon (carbon 2)
CH3-(CH2)x-CH2-CH2-C-S-CoA
Fatty acyl CoA
Acyl CoA dehydrogenases (a family of chain-length–specific enzymes)
FAD
FADH2
CH3-(CH2)x-CH=CH-C-S-CoA
trans-2-Enoyl CoA
2,3-Enoyl CoA hydratase
H2O
OH
CH3-(CH2)x-CH-CH2-C-S-CoA
3-Hydroxyacyl CoA
3-Hydroxyacyl CoA dehydrogenase
NAD+
NADH + H+
CH3-(CH2)x-C-CH2-C-S-CoA
3-Ketoacyl CoA
β-Ketoacyl-CoA thiolase
CoA
CH3-(CH2)x-C-S-CoA + CH3-C-S-CoA
Fatty acyl CoA
Acetyl CoA

(Figure 4)

Energy yield from fatty acid oxidation

The energy yield from the β – oxidation pathway is high, for example, the oxidation of a molecule of palmitoyl CoA to CO_2 and H_2O produces 8 acetyl CoA, 7 NADH, and 7 FADH2, from which 131 ATP can be generated.

The activation of the fatty acid requires 2 ATP, therefore the net yield from palmitate is 129 ATP **(Figure 5).**



(Figure 5)

H.W. 1 / Calculate the energy yield from the oxidation of a molecule of stearic acid (18C).

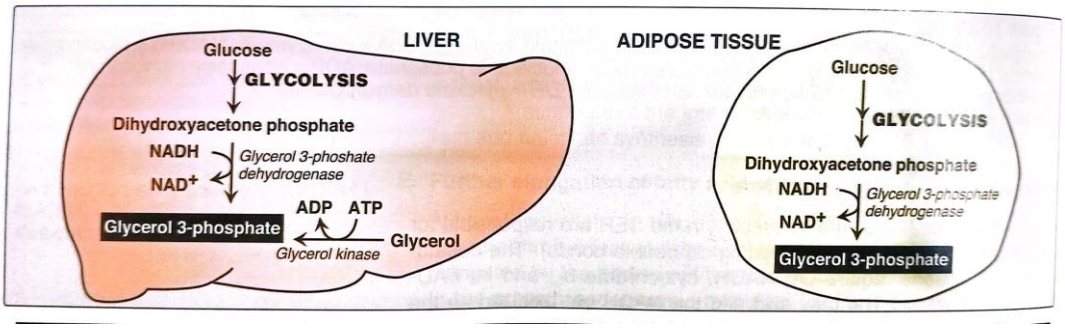
Differences between F.A. oxidation (β-oxidation) and F.A. synthesis(lipogenesis):

(Table 1)

	F.A. Synthesis	F.A. Oxidation
Site	Cytoplasm	Mitochondria
Intermediates	Covalently linked to SH group of ACP	Present as CoA derivatives
Enzyme	Multi-enzyme complex	Present as independent proteins
Co-enzymes	NADPH	NAD^+ and FAD
Product of pathway	Palmitate	Acetyl CoA

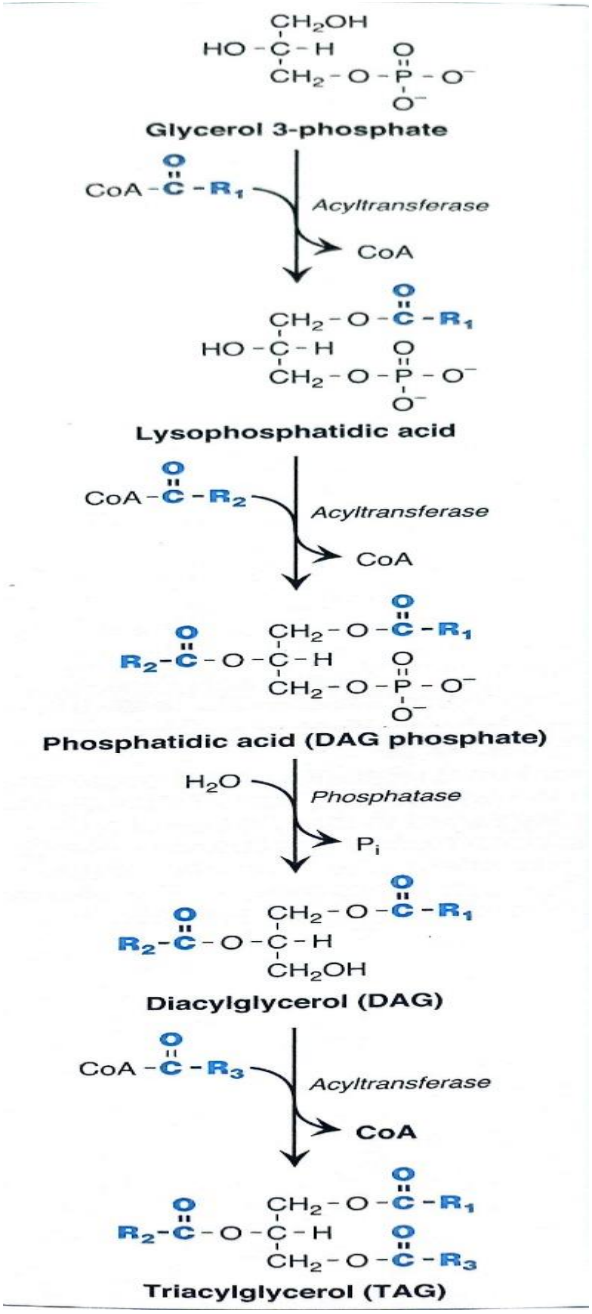
Synthesis of Acylglycerol

1. Glycerol-3-phosphate is the initial acceptor of fatty acids during TAG synthesis. There are two pathways for its production **(Figure 6)**. In both liver (the primary site of TAG synthesis) and adipose tissue, glycerol-3-phosphate can be produced from glucose, by glycerol-3-phosphate dehydrogenase, the second pathway found in the liver, but not in the adipose tissue, uses glycerol kinase to convert free glycerol to glycerol phosphate.



(Figure 6)

2. From glycerol-3-phosphate and fatty acyl coenzyme involve four reactions these include the addition of two fatty acids from fatty acyl CoA, the removal of phosphate, and the addition of the third fatty acid. (Figure 7)



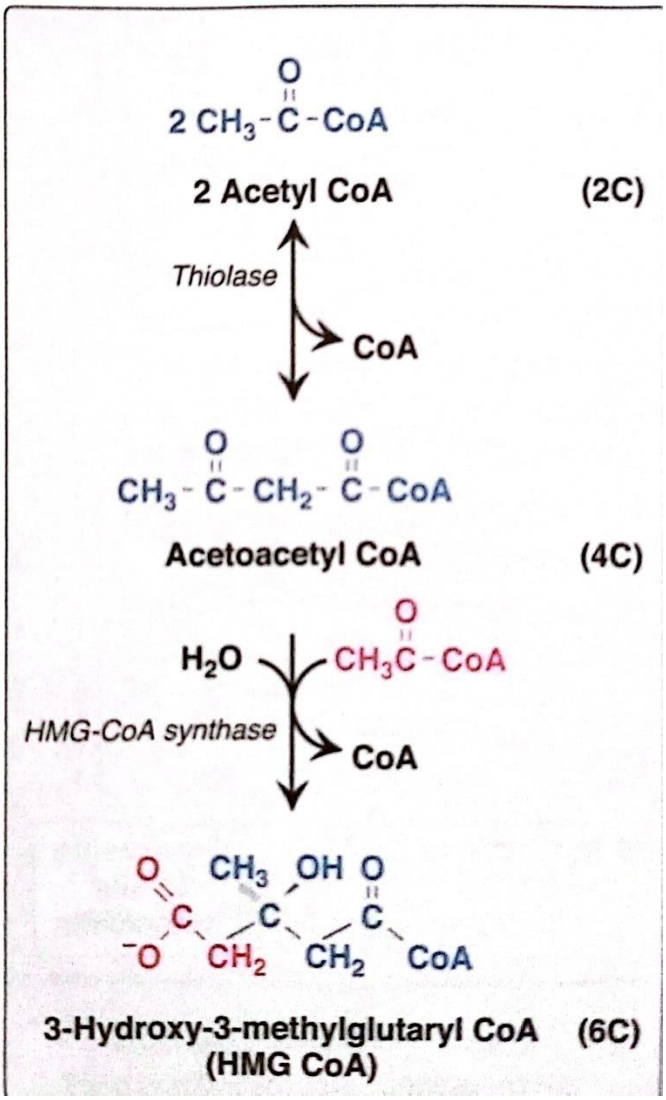
(Figure 7)

Synthesis of Cholesterol

Cholesterol is synthesized by all tissue in human,

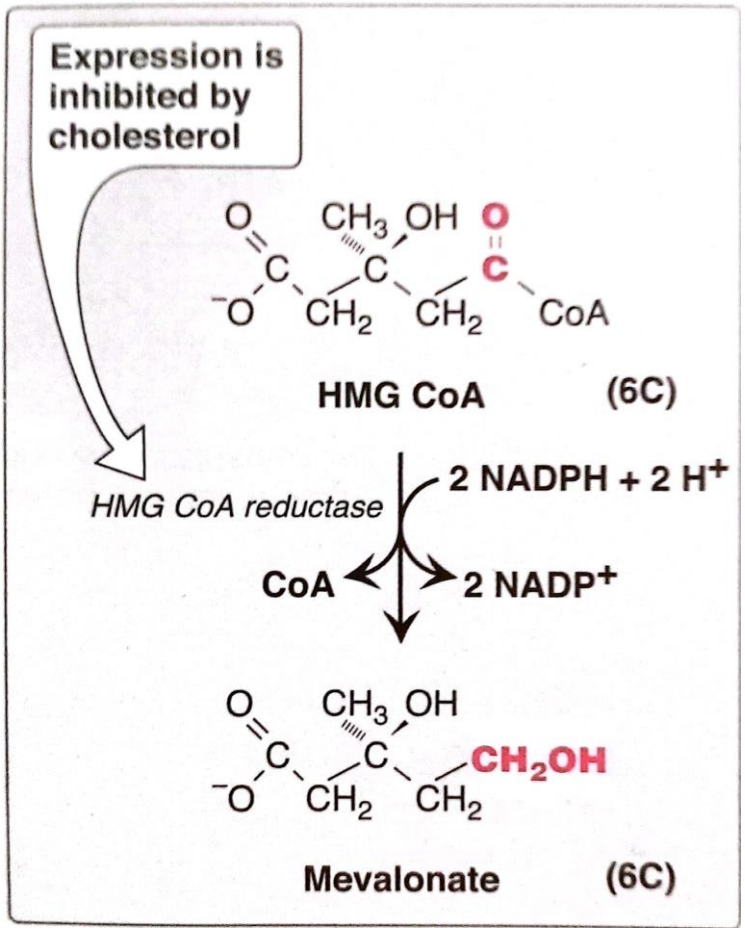
First, two acetyl CoA molecules condense to form acetoacetyl CoA.

Next, a third molecule of acetyl CoA is added by HMG CoA synthase, producing 3-hydroxy-3-methylglutaryl CoA (HMG CoA), a six-carbon compound. **(Figure 8)**



(Figure 8)

The next step**,** the reduction of HMG CoA to mevalonate, is catalyzed by HMG CoA reductase and is the rate-limiting and key regulated step in cholesterol synthesis. **(Figure 9)**



(Figure 9)

[1] Mevalonate is converted to 5-pyrophosphomevalonate in two steps, each of which transfers a phosphate group from ATP.

[2] Isopentenyl pyrophosphate (IPP), is formed by the decarboxylation of 5-pyrophosphomevalonate.

[3] IPP is isomerized to 3,3-dimethylallyl pyrophosphate (DPP).

[4] IPP and DPP condense to form ten-carbon geranyl pyrophosphate (GPP).

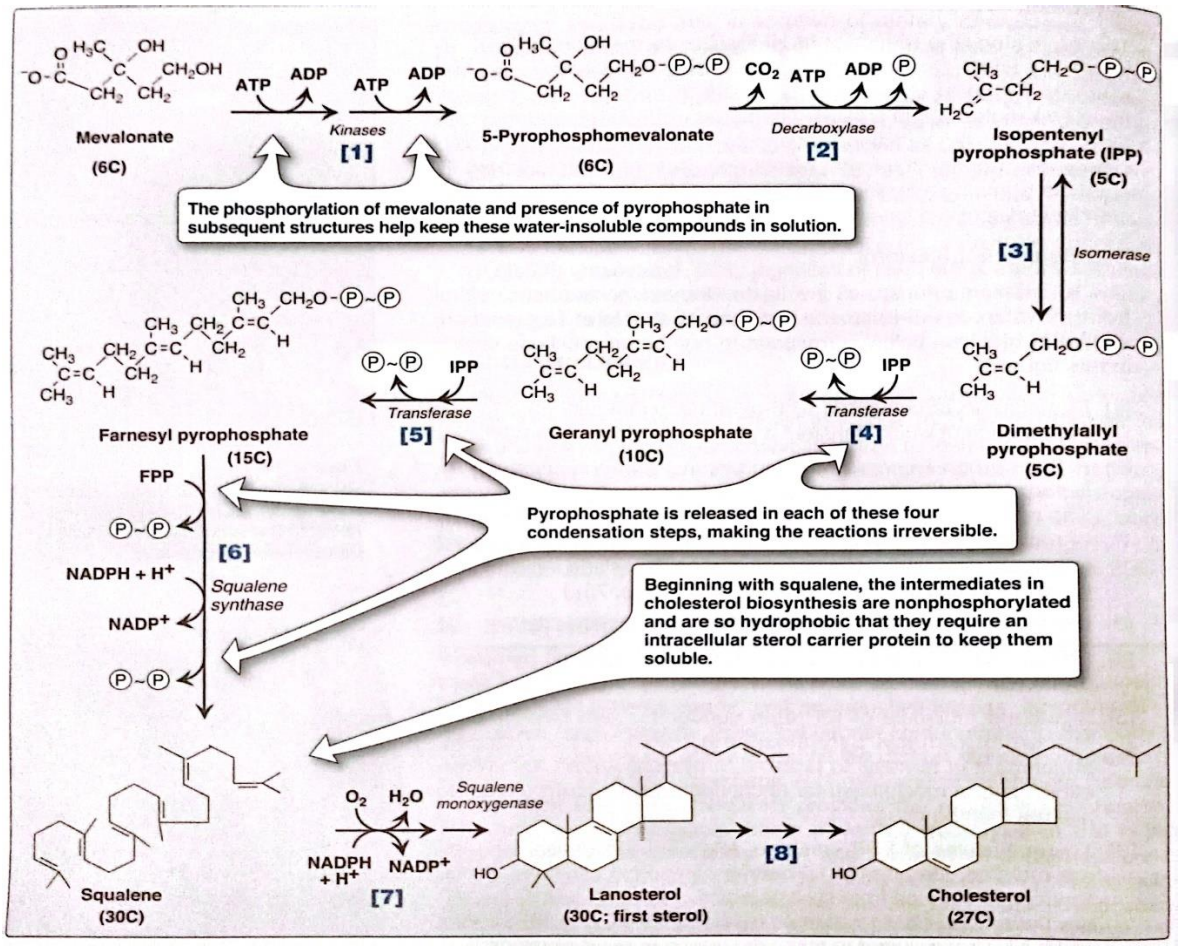
[5] A second molecule of IPP then condenses with GPP to form 15-carbon farnesyl pyrophosphate (FPP).

[6] Two molecules of FPP combine, releasing pyrophosphate, and are reduced, forming the 30-carbon compound squalene.

[7] Squalene is converted to the sterol lanosterol by squalene monooxygenase.

[8] The conversion of lanosterol to cholesterol is a multistep,

- Oxidation removal of methyl groups.
- Reduction of double bond.
- Migration of a double bond. **(Figure 10)**



(Figure 10)

Fat transport and storage in the body

1. **Fat transport in the body:** fats are insoluble in water, they are transported in the blood with the help of lipoprotein, which include:

- Chylomicrons: these carry dietary fats absorbed from the intestines to the liver and adipose tissues.
- Very Low-Density Lipoproteins (VLDL): transport triglycerides from the liver to various tissues.
- Low-Density Lipoproteins (LDL): known as “bad cholesterol” because its carry cholesterol to cells and can accumulate in arteries.
- High Density Lipoproteins (HDL): known as “good cholesterol” because its transport excess cholesterol to the liver for excretion.

2. **Fat storage in the body:**

- Adipose tissue: this is the primary storage site for fats, consisting of adipocytes that store fats as triglycerides.
- Liver: it stores fats and also released when energy is needed.
- Muscles: Contain small amounts of fats used as energy source during physical activity.