LIPID METABOLISM

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Contents

1. Anabolism

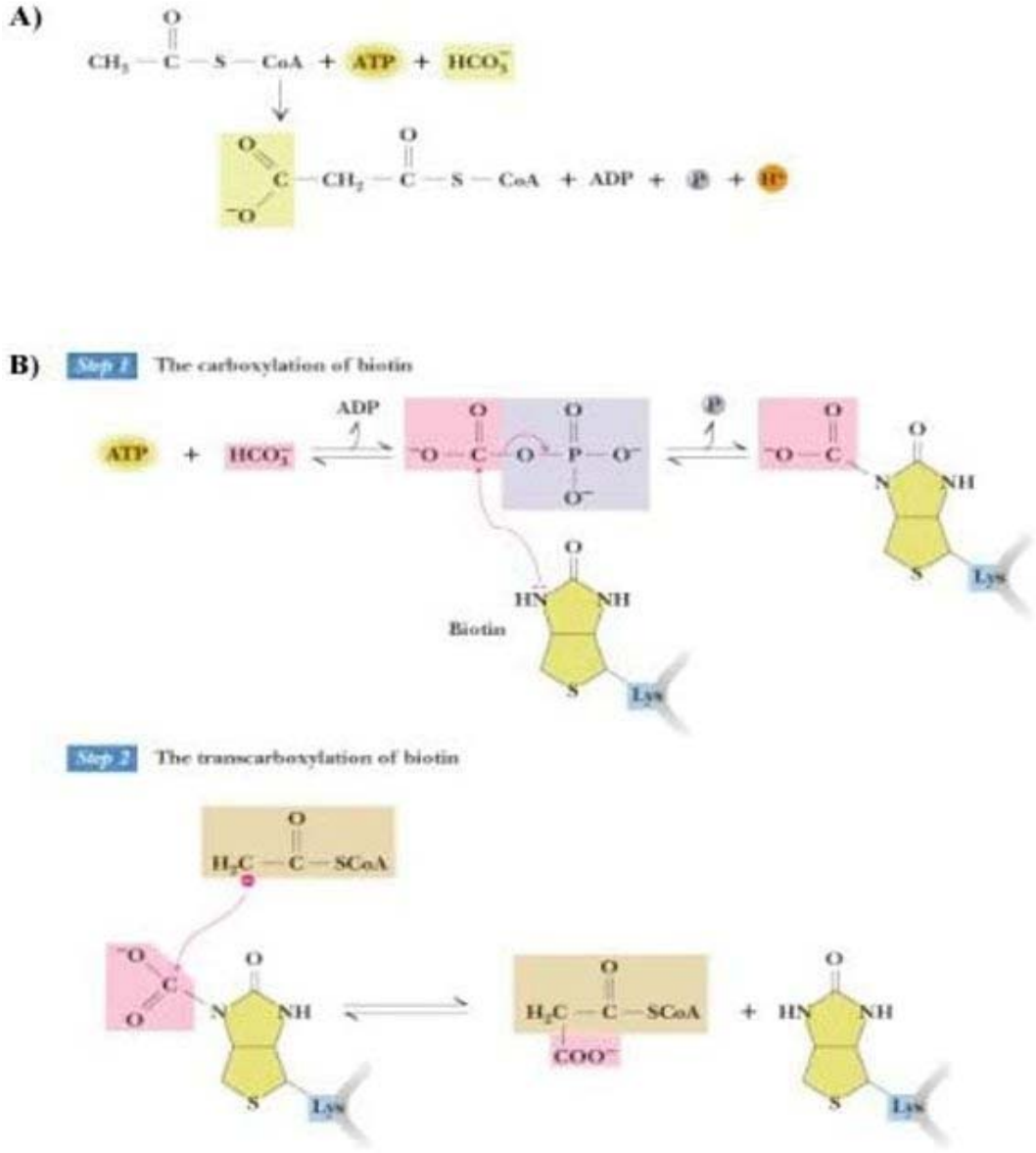

Figure 1:

Fatty acids are built up from mitochondrial 2-carbon acetyl CoA molecules, which have been formed by the oxidative decarboxylation of pyruvate, an end product of aerobic glycolysis. The coenzyme A portion of the acetyl CoA cannot cross the mitochondrial membrane and only the acetyl portion is transported to the cytosol in the form of citrate produced by the citrate synthase mediated condensation of oxaloacetate and the acetyl CoA. The citrate, now in the cytosol, is cleaved by citrate lyase to produce cytosolic acetyl CoA and oxaloacetate. The energy for the carbon-carbon condensations in fatty acid synthesis is supplied by the process of carboxylation, of acetyl CoA into malonyl CoA, and then the decarboxylation of malonyl CoA into acetyl CoA. The enzyme acetyl CoA carboxylase along with the cofactor biotin are responsible for the carboxylation of acetyl CoA into malonyl CoA; Figure 1. Initially the bicarbonate combines with ATP to produce an activated phospho-carbonate anhydride that is able to carboxylate biotin, covalently bound to a lysine residue of the carboxylase enzyme. The carboxyl group is then transferred to acetyl CoA thus producing malonyl CoA.

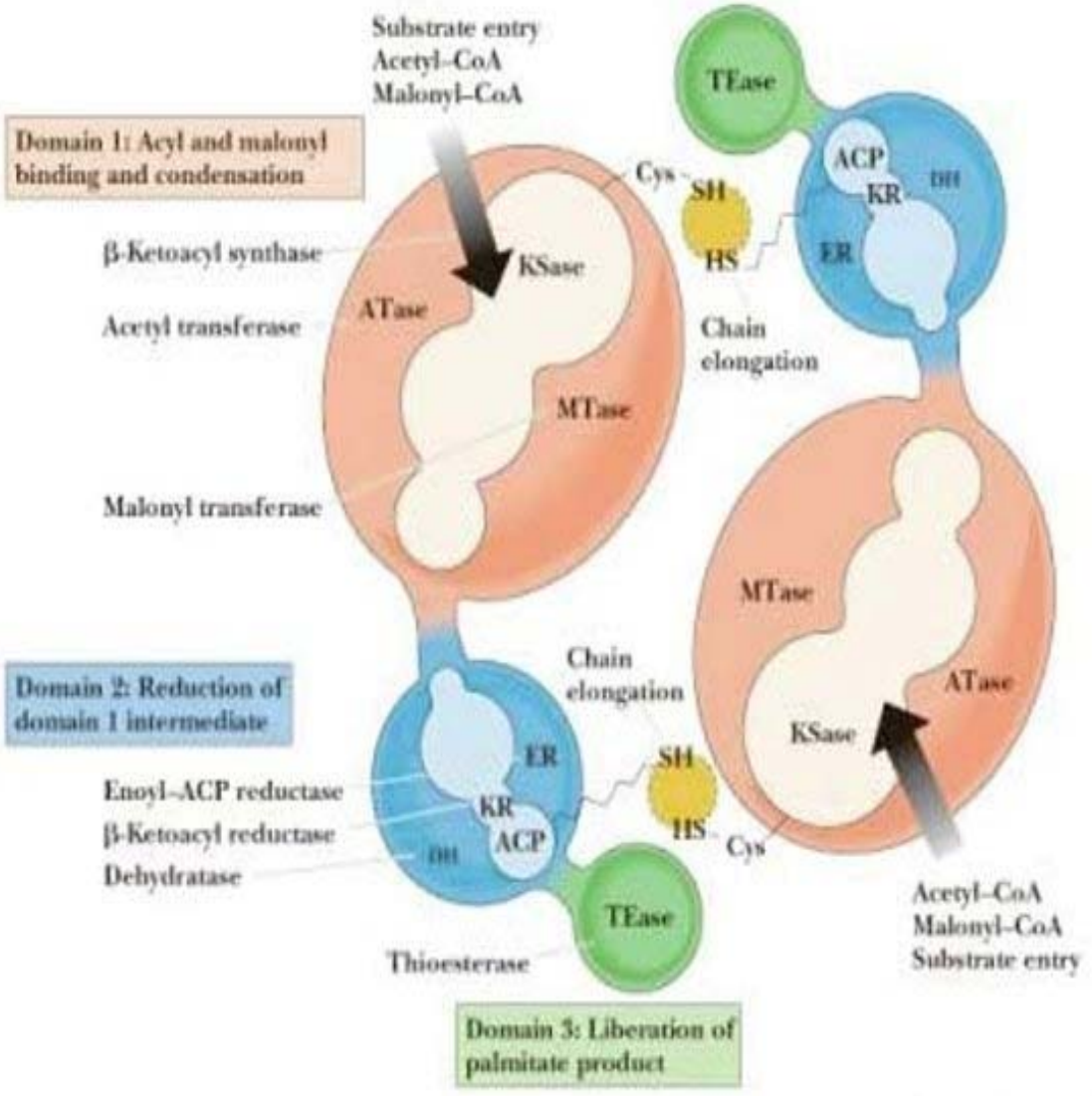

Figure 2:

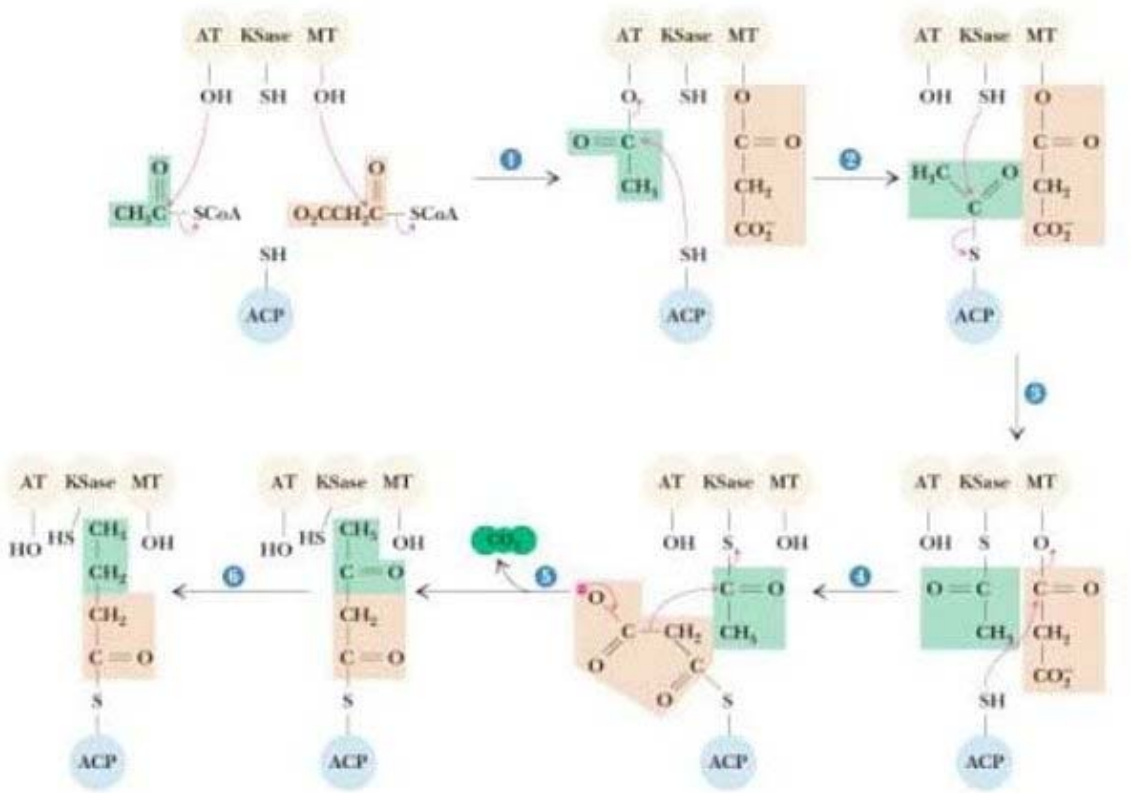

Figure 3:

The remaining series of reactions of fatty acid synthesis is catalyzed by a multi-enzyme complex called fatty acid synthase. This enzyme is dimeric each monomeric unit made up of seven components. [Figure 2] The acetyl CoA and malonyl CoA units are covalently bound through serine residues at the active sites of acetyl and malonyl transferase respectively. Two SH groups play important roles – one as the pantothenic moiety of coenzyme A on an acyl-carrier-protein (ACP) and the other as a cysteine aminoacid at the active region of β-ketoacyl-ACP-synthase. The ACP-SH first transfers the 2-carbon acyl group from acetyl CoA (attached to the serine of acetyl transferase) to the SH group of the β-ketoacyl-ACP-synthase and then, secondly, combines with the 3-carbon unit [OOC-CH_2-CO] attached to a serine of malonyl transferase; Figure 3. A decarboxylation and condensation of this generated 2-carbon unit with the 2-carbon unit on the β-ketoacyl-ACP-synthase yields a 4-carbon acetoacyl grouping attached to the sulphur atom of the acyl-carrier protein (ACP).

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