

Hello students, welcome to module number 16 on anabolism. Biosynthesis of saturated fatty acids part one from Unit 3, chemoheterotrophic lipid metabolism.

Outline is Citric Oxaloacetate shuttle, Regulation of fatty acid biosynthesis.

Learning outcomes: The student will be able to describe citrate oxaloacetate shuttle, explain the activation of intermediates or fatty acid biosynthesis and regulation of fatty acid biosynthesis.

In previous modules You learned about something called beta oxidation, which deals with the degradation of a lipid. Now in this particular module, you will learn something which is the exact opposite of beta oxidation. That is nothing but the biosynthesis of fatty acids. So before we go into the synthesis part, let's quickly recall what fatty acids are. So fatty acids are the simplest lipid. They are hydrophobic in nature and they are made up of long chains of carbon with a single carboxylic group at one end. They usually are 4 to 36 carbons long. Fatty acids can be broadly classified into saturated and unsaturated fatty acids. So unsaturated fatty acids have one or more double bonds, whereas saturated fatty acids have no double bonds present in the chain. The general formula for saturated fatty acid is $\text{CH}_3-(\text{CH}_2)_n-\text{COOH}$, where n represents the number of methylene groups. n differs from one fatty acid to another and accordingly they are given names.

In eukaryotes and in prokaryotes, both the cases fatty acid biosynthesis occur inside the cytoplasm and the precursor for fatty acid biosynthesis is Acetyl CoA. In the case of prokaryotes, since fatty acid biosynthesis occurs inside the cytoplasm, there is not a problem. It can directly enter into fatty acid biosynthesis. But when it comes to eukaryotes Acetyl CoA synthesis occurs exclusively in an organelle called as a mitochondria. So suppose fatty acid synthesis has to occur in eukaryotes this Acetyl CoA has to be transported from mitochondria into the cytoplasm. But the problem is that the inner membrane of mitochondria is impermeable to Acetyl CoA. This is because Acetyl CoA does not have a specific transporter present in the inner membrane of mitochondria. So this problem is solved by something called a citrate oxaloacetate shuttle. So this is a system which helps in the transport of Acetyl CoA from mitochondria into the cytoplasm in case of eukaryotes. So inside the cell the sources of Acetyl CoA are either pyruvate or amino acids. Once the Acetyl CoA is formed, it reacts with the oxaloacetate inside the mitochondria. This reaction is catalyzed by citrate synthase, leading to the formation of citrate. This is the step which is present in the TCA cycle. So when citrate is present in excess, it is transported into the cytoplasm via citrate transporter. So once it is in the cytoplasm, citrate is broken down into Acetyl CoA and oxaloacetate. This reaction is catalyzed by citrate lyase. It requires the consumption of ATP. Now a Acetyl CoA is in the cytoplasm, so it can be directly utilized for the fatty acid biosynthesis. But what happens to the oxaloacetate? When more and more citrate is transported into the cytoplasm, oxaloacetate concentration inside the cytoplasm will go on increasing. so it is important to transport this oxaloacetate back into the mitochondria. So this occurs via two steps. In the first step, Oxaloacetate is converted into malate by malate dehydrogenase. Then Malate is transported via specific transporter into the mitochondrial matrix. In the mitochondrial matrix, Malate is converted into the oxaloacetate by Malate dehydrogenase. Now Oxaloacetate can continue the cycle. The 2nd way by which oxaloacetate can be transported back is the conversion into pyruvate by Malic Enzyme, so Pyruvate also has a specific transporter present in the inner membrane, so it can be transported back into the mitochondria. So once it is in the mitochondria, pyruvate can be back converted into oxaloacetate. It is one of the anaplerotic

reactions catalyzed by pyruvate carboxylase. OK, so to summarize about this Citrate Oxaloacetate shuttle, it has two advantages. One advantage is that it transports the Acetyl CoA from mitochondria into the cytoplasm and the 2nd second advantage is the formation of NADPH. So this NADPH can then participate in the fatty acid biosynthesis.

So once Acetyl CoA is into the cytoplasm, it can now enter into the fatty acid biosynthesis. So the first step in the fatty acid biosynthesis is conversion of Acetyl CoA into two Malonyl CoA. So this particular reaction occurs at the expense of ATP utilizing the bicarbonate and it is catalyzed by Acetyl CoA Carboxylase. It is also abbreviated as ACC. Now this particular step is a committed and irreversible step. It is called irreversible because Malonyl CoA cannot be converted back into Acetyl CoA, and it is called as a committed step because once Acetyl CoA forms the Malonyl CoA catalyzed by ACC, it cannot enter into any other pathway. It will undergo only fatty acid biosynthesis. That's why it is called a committed step. So this particular step will be subjected to the regulation that we will see in the next slides. So this particular enzyme has a prosthetic group, which is a biotin. Once Malonyl CoA is formed, it is then converted into malonyl ACP by the enzyme Malonyl transacylase. So in this particular reaction the Co A is replaced by something called as ACP, giving rise to Malonyl ACP. So these are the first 2 steps. In the third step, what happens is Acetyl CoA gets converted into Acetyl ACP. This reaction resembles step 2. It is catalyzed by transacetylase.

OK. Now coming to the regulation of fatty acid biosynthesis, I told you the reaction which is catalyzed by ACC, is a committed and irreversible state, so it undergoes a strict regulation. It has activators such as abundant nutrients and ATP, citrate, insulin. And the inhibitors of this enzyme include low nutrients and AMP, palmitoyl CoA, Glucagon, and Epinephrine. Out of this, Insulin, Glucagon and epinephrine these are the hormones and which are present only in the higher mammals in the eukaryotes. Whereas the remaining are present in both prokaryotic and eukaryotic microorganisms.

So how do these molecules actually control the ACC? we will see that. We will start with the citrate and high nutrient. So when the cell is growing in the presence of a high concentration of nutrients then in that case, a large amount of citrate will be produced inside the cell. So when citrate is in excess, it activates the ACC by carrying out its polymerization. So when ACC is activated, it can convert acetyl CoA into malonyl CoA. Whereas in contrast when low nutrients are present, low nutrients meaning low ATP. So when ATPs are present low, the concentration of AMP would be high. So under such conditions, the activation of AMPK occurs. AMPK is a type of a kinase which carries out the phosphorylation of ACC. So phosphorylation, meaning it adds a phosphate group to an enzyme ACC. So in this phosphorylated state ACC exam gets inhibited so Acetyl CoA can not get converted into malonyl Co A. The next inhibitor is palmitoyl CoA. Palmitoyl CoA is the end product of fatty acid biosynthesis so when it is in excess, it causes the depolymerization of ACC and depolymerized ACC is inactive so it cannot convert the Acetyl CoA into Malonyl CoA. So this is how these molecules regulate the ACC enzyme and also fatty acid biosynthesis. So these are my references. Thank you.