Biochemistry 401 Lecture 27.
Today we're going to talk about some additional topics in fatty acid oxidation. These include the catabolism of odd-numbered fatty acids and the catabolism that occurs in peroxisomes. We're then going to turn to the glyoxylate cycle and then fatty acid synthesis. This is going to include both the synthesis of saturated fatty acids and unsaturated fatty acids. We're then going to turn to fatty acid synthesis. This includes the synthesis of saturated and unsaturated fatty acids. And finally were going to talk about the regulation of fatty acid metabolism, both the regulation of fatty acid degradation and fatty acid synthesis. So let's get started.

What about fatty acids with odd numbers of carbons? Well, fatty acid catabolism will proceed as normal, releasing two carbons at a time, until the very last round of beta-oxidation, leaves a three-carbon fatty acid proprionyl CoA. This proprionyl CoA will be used to synthesize succinyl CoA in three steps.

The first step is a carboxylation. We're going to add carbon in an ATP-dependent carboxylation using biotin. We end up with D-methylmalonyl CoA and we're going to racimize that from D- to L-methylmalonyl CoA, and then finally we're going to rearrange this molecule to make succinyl CoA. Now, this step involves an intramolecular reconfiguration, and this is a big job, and so we're going to use a big cofactor, cobalamin, B12. Now this is a process that involves some radical chemistry, and finally we're going to end up with succinyl CoA that can enter the TCA cycle. So let's look at each of these individual steps one by one

..and we'll start with an overview of what cobalamin is. Cobalamin is a large complex ring structure prosthetic group that contains a central cobalt. This cobalt is organized in the center of a corrin ring that is a lot like the porphyrin rings that we saw previously in that it is comprised of four pyrrole rings. However, these pyrrole rings have different degrees of saturation and different substituents than the porphyrin ring. Additionally, it has another functional group called a benzimidazole ring that helps suppress that a group to function properly. There is a variable region shown here by x. This x can involve different functional groups, one of which is a 5'deoxyadenosyl group that is shown here. Now this prosthetic group is used in reactions that involve difficult rearrangements of configuration, and the one that we're going do to convert methylmalonyl CoA to succinyl CoA, is pretty radical.

This mutase reaction results in intramolecular rearrangement of methylmalonyl CoA. Cobalt allows formation of a free radical that's necessary for this reaction, and the reason that this can occur is that the bond between CH_2 and cobalt is very tenuous, and can be broken easily to yield a radical. This happens through something called a homolytic bond cleavage, and what this means is that one electron stays with the cobalt to reduce it to Co^{2+} and the other one goes with CH_2 to form a 5'deoxyadenosyl radical. This is not the normal heterolytic cleavage in which both electrons go with one or the other bonding partner, but rather it is a homolytic bond cleavage in which one electron goes with one bonding partner and the other one stays with the other binding partner. In this case, we're left with 5'deoxyadenosyl radical and cobalt that is reduced to 2+. It is the ability of cobalamin to form radicals that allows it to function in this mutase reaction.

So now that we have a free radical at the 5'deoxyadenosyl group, what we going to do with it, and how is this going to affect the formation of succinyl CoA? Well the first thing that's going to happen is the radical is going to abstract a hydrogen atom from the methyl group of L-methylmalonyl CoA to form a CH_2 radical there. This is going to spontaneously rearrange, such that the carboxyl CoA is going to migrate to the site where the radical is, and the electron is going to migrate to where the carboxylate coenzyme A was. This is the intramolecular rearrangement, and it happens spontaneously after radical formation. Finally, this radical will abstract a hydrogen atom from 5'deoxyadenosine to form a 5'deoxyadenosine radical again. To reconstitute the functional enzyme, this radical will form a covalent bond to cobalt in the corrin ring, and so from an L-methylmalonyl CoA, we get succinyl CoA. Cobalamin, vitamin B12, is necessary for this reaction, and it involves radical chemistry.

Now we talked about catabolism of fatty acids occurring in the mitochondrial matrix, but it also can occur in peroxisomes in mammals, and it occurs exclusively in peroxisomes in plants and in yeast, rather than the mitochondria. Now the peroxisome is bounded by a single membrane, and this organelle is thought to arise from the endoplasmic reticulum. There are many enzymes that are found here that catalyze reactions that result in the production of peroxides, H_2O_2. In mammals, long chain fatty acids are catabolized here to form shorter octanoyl fatty acid chains that can then go to the mitochondrion for further degradation.

In this side we see the first cycle of fatty acid breakdown as it occurs in peroxisomes. It's different from what we see in mitochondria. In this pathway, acyl CoA dehydrogenase uses FAD to oxidize the acyl group to yield a double bond. In the process, $FADH_2$ is generated. This $FADH_2$ passes its electrons off to molecular oxygen to form peroxide, and then an enzyme called catalase can actually break down this peroxide to form water and one half O_2. The fatty acyl intermediate can then go on through further oxidations that are very similar to those that we see in the beta-oxidation that occurs in mitochondria.

Now in plants, and yeast, acetyl CoA units can enter something called the glyoxylate cycle. This is similar to the citric acid cycle in some ways, as it involves similar enzymes. However, there's one main difference. We're not going to do any decarboxylations. We're going to start with acetyl CoA and oxaloacetate, using the enzyme citrate synthase, to form citrate. We're then going to do the molecular rearrangement, using aconitase that we saw in the TCA cycle. But this is where the steps differ. Once we get to isocitrate, we're going to use an enzyme called isocitrate lyase that breaks apart isocitrate to form succinate and glyoxylate. Now succinate, as you'll recall, is a four-carbon molecule. Glyoxylate is a two-carbon molecule. The succinate that's generated can go on to make glucose and so in plants, and in yeast, we can use acetyl CoA to form succinate, which can then form glucose. Since mammals do not have the glyoxylate cycle we cannot use acetyl CoA to synthesize glucose, because the carbons that we put into the TCA cycle do not result in a net synthesis of a four-carbon molecule, because the six carbon molecule that we create is converted into a five-carbon and then a four-carbon molecule through oxidative decarboxylation in two steps. Because of the decarboxylations, there is no net synthesis of a four-carbon molecule. So now anyway, since we have glyoxylate, what can we do with that? Well we can add another two carbons to acetyl CoA, and through the use of malate synthase, make malate again. Malate can be oxidized by NAD^+ to form oxaloacetate and NADH, and then we can start the cycle over again. And so again, some organisms do have the glyoxylate cycle, by which they can use the acetyl CoA that's generated in fatty acid breakdown directly to make glucose, through the formation of the succinate intermediate. This four-carbon molecule can then be used to make pyruvate and go on through the gluconeogenic pathway to form glucose.