Biochemistry 401 Lecture 28.
Today we're going to continue our discussion of lipid metabolism. We're going to talk about triacylglycerols and membrane lipids. We're going to discuss the synthesis of triacylglycerols, phospholipids, and glycolipids, and then we'll finish with aberrant lipid synthesis and disease.

So let's first talk about the nature of membrane lipids. Membrane lipids are amphipathic. They have a hydrophilic region and a hydrophobic region. The hydrophilic region is the head group. Head groups extend outward from the membrane to make contact with the aqueous solution, whereas the hydrophobic region, generally hydrophobic fatty acid tails, extend inward toward the center of the membrane, away from aqueous solution. Membrane lipids have a great deal of variety, both in the nature of the head groups, and the hydrophobic region. Let's look at the classification of membrane lipids

There are three major classes of membrane lipids. These are sterols, phospholipids, and glycolipids. Now in animals, the sterol is cholesterol, and this is the ring structure that's shown here in the upper left. Now phospholipids and glycolipids are organized into these groups because of their polar head group. Phospholipids contain a phosphate group, to which is attached an alcohol. Glycolipids, on the other hand, contain one or more sugars as their polar head group. Phospholipids contain one or more fatty acids, and this depends on the type of platform that's used. A glycerol backbone, such as is shown in the upper right-hand corner, will have two fatty acids esterified to the backbone, whereas a sphingosine phospholipid, shown in the middle, will have one fatty acid attached to the amino group of the sphingosine backbone. Now in animals, glycolipids are exclusively formed on a sphingosine backbone, and therefore they will have one fatty acid tail attached to the sphingosine at the amino group, but in plants, there are some glycolipids that also have a glycerol backbone and in this case we'll have two fatty acids attached to the glycerol backbone and one or more sugars as the polar head group. Now sphingosine is shown here. It has three basic characteristics, a long hydrocarbon tail that helps to anchor it into the membrane, an amino group, which serves as the point of attachment for the other fatty acid, and a terminal hydroxyl that's shown on the far right, and this is the place where the phosphate group, or the sugar, is going to be added. We're going to look at the synthesis of each of these classes of membrane lipids. We're going to talk about cholesterol synthesis in another lecture, but in this lecture we're going to talk about the synthesis of phospholipids and glycolipids.

Here is a chart that shows the classification of membrane lipids in plants and animals, and it's here to help you study.

So now let's talk about the synthesis of triacylglycerols and phosphoglycerolipids. These are going to use an activated precursor, phosphatidate. This is an activated diacylglycerol precursor. It consists of a glycerol backbone, to which are attached two fatty acids, These are attached to carbon number one and carbon number two, through ester linkages. At carbon number three, there is a phosphate group. And so another name for this and so another name for phosphatidate is diacylglycerol 3-phosphate. Now if you'll notice, the fatty acid attached to carbon number one is saturated, and the fatty acid attached to carbon number two is unsaturated, and generally, this is what we see. Phosphatidate is an important precursor, so let's look at how it's synthesized.

This is a pretty complex slide, and we're going to break it down.

The synthesis of phosphatidate occurs in the endoplasmic reticulum of liver cells, and it happens by two main pathways, by the de novo pathway and the salvage pathway. Now the *de novo* pathway requires glycerol 3-phosphate and free fatty acids. The glycerol 3-phosphate is produced either from dihydroxyacetone phosphate or from glycerol.

And so I have a question for you, what kind of reaction would it take to be able to go from dihydroxyacetone phosphate, which is a phosphorylated three-carbon ketone sugar, to glycerol 3-phosphate, and again how do we go from glycerol to glycerol three-phosphate? What sort of an enzyme would do this reaction?.....

We're going to reduce dihydroxyacetone phosphate in order to make glycerol three-phosphate, and the source of the electrons is NADH, and we're also going to add a proton. If you figured this out, very good. Another question where did we see this before? This is part of the glycerol 3-phosphate shuttle.

It's one of the ways to get reducing equivalents into the mitochondrial matrix, and so this cytoplasmic enzyme also is used to produce glycerol 3-phosphate for the production of triacylglycerols and glycerophospholipids.

Okay, now what about taking glycerol and producing glycerol 3-phosphate? How is that?

This is a simple kinase reaction. We're going to phosphorylate glycerol at position three to make glycerol 3-phosphate. That's pretty simple. So in adipose tissue diagrammed on the left, triacylglycerols are catabolized to release free fatty acids and glycerol. Now he glycerol travels in the blood to the liver and in liver cells the glycerol kinase produces glycerol 3-phosphate. So why do we have to transport the glycerol all the way to the liver? The activity of glycerol kinase in the adipose tissue is very slight compared to what's in the liver. In fact, in the liver cells, glycerol kinase is 200 to 600 times more active than in adipose tissue.

So now that we have glycerol 3-phosphate, and we produced free fatty acids from the breakdown of triacylglycerol in the adipose tissue, or in the diet, we can then transport those intermediates to the liver, and in the endoplasmic reticulum of liver cells, we can synthesize phosphatidate.

We're going to add two fatty acids, the first one at position one, and the second one at position two. These fatty acids aren't just fatty acids on their own. They're activated fatty acids. Each one is a fatty acyl-CoA, and the enzyme that catalyzes these reactions is glycerol phosphate acyltransferase, and this name makes sense, because this process transfers a fatty acyl group from the thiol ester of coenzyme A to form an oxygen ester, first to make lysophosphatidate and then finally to make phosphatidate. You do not have to remember the name of the intermediate, lysophosphatidate. And so at the end of these two acylations, we end up with the acylated, activated glycerol intermediate, phosphatidate,

And in the endoplasmic reticulum of the liver, this phosphatidate is going to be turned into either triacylglycerol or glycerophospholipids. Let's look at how that's done. Let's take a look at the synthesis of triacylglycerols first.