Biochemistry 401 Lecture 29.
Today we're going to talk about cholesterol. We're going to talk about the function of cholesterol first, and then the synthesis, the regulation, and some cholesterol derivatives, and this will include the function and the synthesis of these derivatives. So let's get started.

Cholesterol is a steroid consisting of four rings and a hydrophobic tail. It is a very planar molecule and hydrophobic. It functions as a membrane lipid to modulate membrane fluidity and it's also found in lipid rafts. It is a precursor for synthesis of steroid hormones, of bile salts, and also of vitamin D.

Now cholesterol can be transported in lipoproteins, and can be stored in the cell, but to do so, we're going to hide the polar hydroxyl, because that is the only polar group in the whole molecule, and we're going to hide that by adding a fatty acid through esterification. We're going to make an ester linkage between the fatty acid and cholesterol, to make a cholesterol ester. This is going to increase the hydrophobicity of cholesterol, and allow it to pack even tighter into a smaller area for storage in the cell, or for transport. In membranes, the polar hydroxyl group is important. It's oriented towards the aqueous environment and interacts with polar head groups of membrane lipids, and water molecules.

There are two sources of cholesterol, dietary cholesterol and endogenous cholesterol. Dietary cholesterol is ingested in the foods that we eat. It's packaged into transport micelles, and this happens in the intestines. These micelles are also called chylomicrons. Endogenous cholesterol, on the other hand, is synthesized *de novo.* It is packaged up in the liver into transport units called very low density lipoprotein particles that include both lipid and protein, and we'll talk about both of these later on in more detail.

Here we see a brief overview of the steps involved in cholesterol synthesis. There are five important steps. Step one is a condensation of three activated acetyl units to form the six-carbon molecule, HMG-CoA. Step number two is the reduction of HMG-CoA to form mevalonate. Step number three is decarboxylation to the five-carbon activated isoprenyl unit, isopentenyl pyrophosphate. Step four is the condensation of six activated isoprenes, both isopentenyl pyrophosphate and its isomer, dimethylallyl pyrophosphate, to eventually form the 30 carbon unit, squalene. This happens first through the formation of geranyl pyrophosphate, 5 + 5 = 10, and geranyl pyrophosphate has 10 carbons. We're then going to add another five carbons to geranyl pyrophosphate to yield farnesyl pyrophosphate. Farnesyl pyrophosphate contains 15 carbons. Then comes the condensation of two molecules of farnesyl pyrophosphate to form squalene. 15+15 = 30 Finally, step number five is a cyclization of squalene to form lanosterol, and then modification in several steps to form the mature cholesterol. We're going to look at these one by one in more detail.

The first reaction that occurs in cholesterol synthesis is a condensation reaction between the four-carbon molecule acetoacetyl CoA and the two-carbon molecule acetyl CoA. This results in the production of 3-hydroxy-3-methyl-glutaryl CoA, HMG C A and release of CoA. Now we've seen HMG CoA before, in the mitochondrion. It's also an intermediate in ketone body synthesis, and so here we see two isozymes of HMG CoA synthase, one in the cytoplasm that functions in the synthesis of cholesterol, and one of the mitochondrion, that's involved in ketone body synthesis. Now in the cytosol, 3-hydroxy-3-methyl-glutaryl CoA is an intermediate in cholesterol synthesis, and is going to be reduced in a series of reactions to yield mevalonate, and the electron carrier in this case is any NADPH So what we're left with are two molecules of $NADP^+$, coenzyme A, and the six-carbon intermediate, mevalonate. Now in the mitochondrion, as we said, 3-hydroxy-3-methyl-glutaryl CoA is an intermediate in the synthesis of ketone bodies, and it's used to make acetyl CoA and acetoacetate you'll recall that acetoacetate is actually ketone body. And so let's go back to the synthesis of mevalonate in cholesterol synthesis in the cytosol. In going from 3-hydroxy-3-methyl-glutaryl CoA to mevalonate, there are two reduction reactions, one to produce an aldehyde, and the second to produce an alcohol. The enzyme that carries out these reductions is HMG CoA reductase, and this name makes sense. This is actually an integral membrane protein that carries out a cytosolic reaction, but the protein itself is anchored to the outside face of the endoplasmic reticulum. HMG-CoA reductase catalyzes the rate-limiting step in cholesterol synthesis. It's the slowest step in the pathway, and therefore it's highly regulated. Now the next step that we're going to see is going to use three molecules of ATP, which is really expensive, and so it's a good idea to make sure that you really want to make mevalonate.

The synthesis of mevalonate represents the rate-limiting step in cholesterol synthesis, and therefore the enzyme that catalyzes this reaction, HMG CoA reductase, is highly regulated.

Here we see figure of one monomer of the tetrameric enzyme, HMG CoA reductase. In eukaryotes, this is an integral membrane protein that's bound to the outer face of the endoplasmic reticulum. This represents one of the most highly regulated enzymes in the human body.

And so from the six-carbon intermediate, mevalonate, we're going to produce the five-carbon activated isoprene unit, 3-isopentenyl pyrophosphate. To do this, were going to use three molecules of ATP. The final step is going to release carbon dioxide, to go from a six-carbon unit to a five carbon unit. One molecule of inorganic phosphate is also going to be released. You do not need to know all of the intermediates between mevalonate and 3-isopentenyl pyrophosphate. You do need to know the starting reactants, which are the six-carbon mevalonate, and three molecules of ATP. You also need to know the final products, which are the five-carbon 3-isopentenyl pyrophosphate, carbon dioxide, and one molecule of inorganic phosphate. Now that we have 3-isopentenyl pyrophosphate what can we do with this? This is a very important intermediate it turns out.

These are some of the derivatives that can be made from 3-isopentenyl pyrophosphate. they include cholesterol of course, but also steroid hormones, bile salts, and vitamins D, A, E,K, which you should recognize as being all of the lipid soluble vitamins also the quinone electron carriers ubiquinol that when all and all calls you are only responsible for those that are bolded and are not responsible for knowing the derivatives that are found in plants.

Isopentenyl pyrophosphate exists in equilibrium with its isomer dimethylallyl pyrophosphate and the difference between these two intermediates is the position of the double bond. Both of these isomers are used in the next step of cholesterol synthesis.

The next series of reactions are driven forward by pyrophosphate hydrolysis, and the first reactions occur through addition of isopentenyl pyrophosphate. Reaction number one condenses dimethylallyl pyrophosphate with isopentenyl pyrophosphate and there is a loss of pyrophosphate. This forms the 10-carbon