Biochemistry 401 Lecture 23
Today we're going to start a discussion of glycogen metabolism. We're going to begin with glycogen degradation. This is the mobilization of glucose to fit the needs of the cell itself, and in some cases the needs of the body as whole. We're then going to talk about glycogen synthesis. This is the formation of the glucose storage unit. So let's get started.

So what is glycogen? Well, glycogen is a highly branched polymer of glucose that's found in organisms such as animals, and also bacteria. It consists of glucose units that are attached through two types of glycosidic linkages. In the straight chains, glucose units are attached to alpha-1,4 linkages, whereas branch points are formed through alpha-1,6 linkages, and branch points are found for about every 10 units in the polymer. Glycogen also includes an initiator primer molecule and this is called glycogenin. This is shown by a yellow circle, with a G in it. This polymer has directionality, such that the reducing ends are attached to glycogenin and the beginning of branches, and the non-reducing ends are found at the ends of branches. And so when glycogen is mobilized, this mobilization occurs at the non-reducing ends, and additional monomers are added to the non-reducing ends.

Now the primary storage sites for glycogen are the skeletal muscles and the liver. Skeletal muscle cells contain glycogen that's used for their own needs. The glycogen stores in muscle cells are approximately 2% by weight. However, liver cells contain glycogen that's used not just for the needs of the liver cell, but for the needs of the body as a whole, and so the percentage of glycogen per cell by weight is higher, 10%. We have more glycogen that's stored in our muscles than we do that's stored in our liver. This is because we have more muscle cells than we have liver cells, but for each individual cell of the muscles we have less glycogen stored per cell, than we have stored per cell in the liver, 2% in an individual muscle cell, versus 10% per individual liver cell. Glycogen is stored as dense granules in the cytoplasm, and this is shown in the electron micrograph to the right. We can see glycogen granules deposited in the cytoplasm. The large circle almost in the center of the micrograph is the nucleus, and mitochondria are the little ovals that are seen in the slide. The dense, dark granules that you see that look almost like freckles in the cell, is the glycogen, and these cells are actually liver cells. But why use glycogen? Why not just use fatty acids and fats as a prime storage molecule? Well, this is because glucose is the sole fuel for red

blood cells, and it is the primary fuel that's used by the brain. When you break down glycogen, you get glucose molecules that can be used by all the tissues in the body, however, if you were to break down fatty acids, you would get acetyl CoA, and this can't be used by red blood cells, and the brain would really rather not use this. It can use breakdown products from fatty acids, if it needs to, under starving conditions, but it is more difficult for the brain to do this. And so the primary circulating fuel is glucose, and the primary storage fuel is glycogen. Also the utilization of glucose can proceed under anaerobic conditions. Also glycogen has many branch points for rapid regulated mobilization, and we'll see this in just a minute.

And so here we see a schematic representation in Haworth diagram of glycogen. The linear straight chains consist of glucose residues that are linked by alpha-1,4 linkage. Branch points are formed through a glycosidic bond between carbon 1 and carbon 6, and so individual branch points are alpha-1,6 linkages, rather than alpha-1,4 linkages.

The glycogen free ends of straight-chain polymers are broken down to release glucose 1-phosphate, and the enzyme that catalyzes this reaction is called glycogen phosphorylase. We're breaking down glycogen into individual glucose 1-phosphate units, and we're doing this by adding phosphate, and so this process is called phosphorolysis. It's because we're using phosphate to break a covalent linkage. This is similar to what we see with hydrolysis, only instead of water, we're using a phosphate. The product of this reaction is glucose 1-phosphate and a polymer reduced in length by one glucosyl unit. Now the glucose 1-phosphate that's liberated can be transformed to a glycolytically usable glucose 6-phosphate, and the enzyme that does this is phosphoglucomutase. And again, the names of these enzymes, both of them, really say what they do. Once glucose 6-phosphate is made, it can go on through glycolysis as we saw before. It can be shuttled off to other tissues. In the liver we can use glucose 6-phosphatase to release free glucose into the bloodstream for use by other tissues. Another thing that we can do with glucose 6-phosphate, is to use this product directly in the pentose phosphate pathway. We haven't talked about this pathway yet, but we will shortly.

And so again there are three fates of glucose 6-phosphate, glycolysis, the generation of free glucose, and the pentose phosphate pathway, and one of the

functions of the pentose phosphate pathway is to make NADPH. Now the fate of glucose 6-phosphate depends on the cell type and the current metabolic needs of the organism.

We're going to take glycogen and use glycogen phosphorylase to release glucose 1-phosphate and a glycogen molecule that's reduced in length by one glucosyl unit. We're then going to use phosphoglucomutase to make glucose 6-phosphate.

Now glycogen phosphorylase cleaves glucose through the addition of inorganic phosphate. This molecule can catalyze phosphorolysis of the straight chains to within four glucosyl units of a branch point. Once it gets too close to a branch point it can't function any longer, because it just doesn't have enough room to function. This enzyme yields alpha glucose 1-phosphate monomers. Now this is an energetically favorable reaction, because the released glucose is already phosphorylated. It's also favorable because this intermediate cannot diffuse out of the cell. Once you've made this phosphorylated glucose, you're not going to lose it. You're not going to lose it to the bloodstream, if you're a muscle for instance.

Now the glycogen phosphorylase enzyme is a dimeric enzyme that cleaves the alpha-1,4 glycosidic bond between carbon number 1, and the glycosidic oxygen, through phosphate addition, and it uses a cofactor called pyridoxal phosphate. It's important to make sure that this is a phosphorolytic not a hydrolytic reaction. We don't want to lose the phosphate to a reaction that is unproductive, and so, in order to do this, we must exclude water from this reaction.

In this diagram, we see a ribbon diagram of glycogen phosphorylase. This enzyme is a homodimer that is allosterically regulated. One subunit is shown in yellow and the other one is shown in white. In the ball and stick diagram to the right, we see pyridoxal phosphate, with inorganic phosphate and glycogen in the active site. This active site is organized so that it excludes water from the site of the reaction. This makes sure that phosphorolysis occurs and not hydrolysis. The enzyme is a processive enzyme. This means it's able to hold on to the glycogen molecule, and cleave one glucosyl residue at a time, without letting go of the glycogen molecule. This enzyme can cleave many residues without leaving the substrate.