The following content is provided under a Creative Commons license. Your support will help MIT OpenCourseWare continue to offer high-quality educational resources for free. To make a donation or view additional materials from hundreds of MIT courses, visit MIT OpenCourseWare at ocw.mit.edu.

PROFESSOR: In this session, we're going to be looking at carbohydrate biosynthesis. Please look at Storyboard 29. Looking at Panel A, the next set of pathways on which we're going to focus concerns carbohydrate biosynthesis.

First, we're going to look at the pathway by which glycogen is made. As you know, glycogen is the polymeric form of glucose that's very readily available for energy production. The second pathway is gluconeogenesis. The organs that utilize glucose as their metabolic fuel prefer to have glucose at a concentration of about 100 milligrams per deciliter in the blood.

The challenge comes from the fact that we eat only sporadically, and thus, levels of glucose will go up and down depending upon the time that has passed since our last meal. When glucose levels drop, gluconeogenesis is the pathway that's activated. It takes non-carbohydrate precursors, converts them to glucose, and then secretes the glucose into the blood, ultimately to help maintain a constant glucose concentration.

Looking at Panel B, our first topic is the synthesis of glycogen. If you look back at my first two lectures, I describe the structure of glycogen, which is also shown here. The piece of glycogen that I've shown consists of a linear chain of glucose molecules connected together through the 1 and 4 carbons. Chemically, we call this an alpha 1, 4 linkage.

To the left of the glycogen molecule is the non-reducing end and to the right is the reducing end, which is connected by a tyrosine residue to a protein called glycogenin. Glycogenin is a variant of the glycogen synthase enzyme we'll talk about later. Glycogenin has the property that it can synthesize a polymeric glucose chain, such as the one shown, to boot up the synthesis of glycogen.

In effect, glycogenin forms a primer molecule such as the one shown that provides a non-reducing end that can be extended by its sister enzyme, glycogen synthase. While I've drawn a linear glucose, I want you to keep in mind, the branches off of the six carbon of the glucoses in the chain are possible. As I mentioned earlier, glycogen is designed for fast breakdown. Its glucose units will quickly enter the pathway of glycolysis and generate ATPs in a manner of seconds.

Let's now look at Panel C. It's useful to review the biochemical steps by which glycogen is broken down because the exact same intermediates appear in the reverse order in the synthesis of glycogen. The key enzyme for glycogen breakdown, or glycogenolysis, is glycogen phosphorylase. Glycogen phosphorylase progressively will nip off the non-reducing end-- that is the left-most sugar as shown-- producing oxonium ion intermediate.

And as we saw in my first lecture, glycogen phosphorylase stereospecifically adds inorganic phosphate to the bottom face-- that is the alpha face of the oxonium ion-- to give glucose 1-phosphate with this stereochemistry shown. Once again, these same intermediates are going to appear in the synthesis of glycogen.

Now let's take a look at the way that glucose 1-phosphate interfaces with the other biosynthetic and catabolic pathways. Let's look at Panel D. This metabolic map shows glycogen in the lower right-hand corner. We can see how glycogenolosis results in glycogen breakdown to glucose 1-phosphate, and in the reverse direction, we can see how glucose 1-phosphate can be used to make glycogen by way of two enzymes-- UDP Glucose Pyrophosphorylase, UGP, and Glycogen Synthase, GS.

Let's look a little deeper at other pathways with which glucose 1 phosphate interfaces. This schematic shows that glucose 1-phosphate can be converted to glucose 6-phosphate by phosphoglucomutase, PGM. In this case, the phosphate is moved from the 1 carbon to the 6 carbon of the glucose moiety. The opposite reaction also occurs. That is, if you have glucose 6-phosphate, phosphoglucomutase will convert it to glucose 1-phosphate.

Glucose 6-phosphate is an intermediate in glycolysis, gluconeogenesis-- which is the next pathway we're going to look at-- and another future pathway, the pentose phosphate pathway. All of this shows us that glucose 6-phosphate is a crossroads and one of the branches that leads from it and it is by way of glucose 1-phosphate. Let's imagine a scenario in which we eat a meal. Glucose appears in the blood as shown. It is taken into the cell. The enzymes hexokinase or glucokinase will phosphorylate the glucose into glucose 6-phosphate. If the glucose is not needed for glycolysis or the other pathways that I mentioned, phosphoglucomutase will convert the glucose 6-phosphate to glucose 1-phosphate, and then in the pathway of glycogen synthesis, glucose 1-phosphate will be polymerized into glycogen for energy storage.

At this point, let's turn to Storyboard 30 and look at Panel A. Now let's take a look at the detail pathway by which glucose 1-phosphate is converted to glycogen. At the left is the structure of glucose 1-phosphate. The first enzyme involved is UDP Glucose Pyrophosphorylase, or UGP. The second substrate in this reaction is UTP, uridine triphosphate.

The UDP Glucose Pyrophosphorylase catalyzes attack by the phosphate on the 1 carbon of glucose 1-phosphate on the alpha phosphorus of UTP. The two products are pyrophosphate and UDP glucose. The reaction is made thermodynamically irreversible by hydrolysis of pyrophosphate by inorganic pyrophosphatase into two molecules of inorganic phosphate. The UDP glucose is the substrate for the next enzyme in the sequenced glycogen synthase.

I'm going to divide the glycogen synthase reaction into two parts. In the first, we see cleavage of the bond between the 1 carbon of the glucose and the beta phosphate of the UDP. This reaction liberates the UDP and generates the oxonium ions shown in the brackets. Structurally, this oxonium ion is the same intermediate we saw in glycogen breakdown, but here, we're using it as a biosynthetic reagent.

Let's look at Panel B. In this panel, we continue the glycogen synthase reaction. In Panel A, we generated the oxonium ion of glucose, which is shown here, in Panel B in the lower left.

Glycogen synthase activates the hydroxyl group on the 4 carbon of the terminal sugar residue. That is the sugar on the non-reducing end. The oxygen on the non-reducing sugar residue of glycogen then attacks the bottom face of the oxonium ion to give rise to a glycogen unit that has been extended by one glucose residue. I have put an asterisk on the 6 carbon of the glucose residue that's been added to the growing glycogen chain.